UNIVERSITY OF MICHIGAN
NOV 21 1956
HOSPITAL LIBRARY

Vol. 232, No. 5 NOVEMBER, 1956 No.

THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

REG. U. S. PAT. OFF.
ESTABLISHED 1820

Editor
RICHARD A. KERN, M.D.

Associate Editor
THOMAS M. DURANT, M.D.

Assistant Editor
CHRIS J. D. ZARAFONETIS, M.D.

Carl Bachman	McKeen Cattell	Harry Gold	C. G. Johnston	C. Thorpe Ray
Herman Beerman	Frank R. Drake	John E. Gordon	John G. McAfee	Roger W. Reed
Wm. L. Benedict	G. Lyman Duff	David M. Gould	A. Harry Neffson	John H. Stokes
A. M. Bongiovanni	Franklin G. Ebaugh	Theodore H. Ingalls	Franklin L. Payne	H. P. Wagener
George E. Burch	Noah D. Fabricant	N. R. Ingraham, Jr.	I. S. Ravdin	Irving J. Wolman

Varicella Pneumonia in Adults. By Reginald H. Fitz, M.D., and Gordon Meiklejohn, M.D. 489

Erythromycin: An Evaluation for Clinical Toxicity. By Mark J. Ciccantelli, M.D., and Mark W. Garry, M.D. 500

The Dynamics of Placebo Therapy: A Clinical Study. By Keith H. Fischer, M.D., and Barney M. Dlin, M.D. 504

Effects of Cortisone on Metabolic Responses in Myocardial Infarction. By Gordan G. Bergy, M.D., Robert W. Burroughs, M.D., and Robert A. Bruce, M.D. 513

Correlation of Pain and the Roentgenographic Findings of Spondylosis of the Cervical and Lumbar Spine. By Allen E. Hussar, M.D., and Emanuel J. Guller, M.D. 518

The Angiocardiographic Pattern of High Ventricular Septal Defect with Left to Right Shunt. By Louis A. Soloff, M.D., and Jacob Zatuchni, M.D. 528

Experimental Myocardial Infarction: Circulatory, Biochemical and Pathologic Changes. By Richard J. Bing, M.D., Alberto Castellanos, M.D., Erich Gradel, M.D., Charles Lupton, M.D., and Abraham Siegel, M.D. 533

Incidence of Coexistent Essential Hypertension and Malignant Neoplastic Diseases. By Phillip J. Moore, M.D., R. D. Taylor, M.D., and A. C. Corcoran, M.D. 555

Spinal Fluid Alcohol in Yeast Meningitis. By Richard Tyler, M.D. 560

The Effect of Hyaluronidase on the Absorption of Subcutaneously Administered Phenol Red. By Eugene A. DeFelice, M.D., R. Richterich-van Baerle, M.D., Robert Megirian, M.S., and Earl H. Dearborn, Ph.D., M.D. 562

Malaria in Veterans of the Korean War: A Review of 128 Admissions for Malaria to a Veterans Hospital. By Robert Schwartz, M.D., and William B. Tuttle, M.D. 568

Radiology

Radiological Diagnosis of Diseases of Adrenal Origin. By John G. McAfee, M.D., and Carl E. Balli, M.D., Baltimore, Maryland 572

Book Reviews and Notices 601

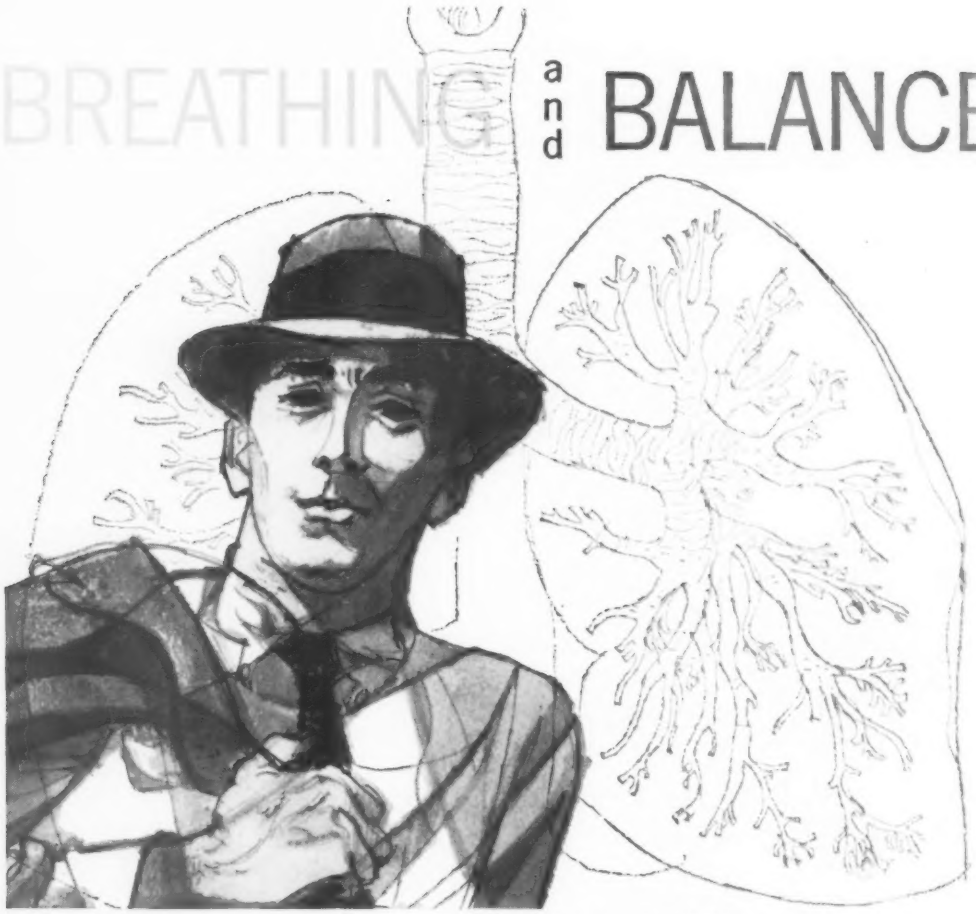
Complete contents on adv. page 8

OWNERS AND PUBLISHERS LEA & FEBIGER PHILADELPHIA 6, PENNA.

Copyright, 1956, by Lea & Febiger. All Rights Reserved. Entered as second-class matter November 5, 1887 at the Post Office at Philadelphia, Pa. under the act of March 3, 1879

PUBLISHED MONTHLY. SUBSCRIPTIONS, TEN DOLLARS A YEAR

BREATHING and BALANCE



in bronchial asthma

Sterane

brand of prednisolone

one of "the best therapeutic agents now available"*

provides restoration of breathing capacity — Relief of symptoms [bronchospasm, cough, wheezing, dyspnea] is maintained for long periods with relatively small doses.*

minimal effect on electrolyte balance — "in therapeutically effective doses . . . there is usually no sodium or fluid retention or potassium loss."* Lack of edema and undesirable weight gain permits more effective therapy particularly for those with cardiac complications

Supplied: White, 5 mg. oral tablets, bottles of 20 and 100. Pink, 1 mg. oral tablets, bottles of 100. Both are deep-scored.

*Schwartz, E.: New York J. Med. 56:570, 1956.

PFIZER LABORATORIES, Brooklyn 6, New York
Division, Chas. Pfizer & Co., Inc.

THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

NOVEMBER, 1956

ORIGINAL ARTICLES

VARICELLA PNEUMONIA IN ADULTS*

By Reginald H. Fitz, M.D.
ASSISTANT PROFESSOR OF MEDICINE

AND

Gordon Meiklejohn, M.D.
PROFESSOR OF MEDICINE

(From the Department of Medicine, University of Colorado School of Medicine, Denver, Colorado)

Pneumonia as a visceral manifestation of chickenpox in the adult has been well characterized both as a clinical and pathological entity. The number of cases reported, however, has been small. Including the initial description by Waring, Neubuerger and Geever in 1942[15] only 15 cases have been reported in the American literature (Bunn and Hammond[2], Claudy[3], Eisenbud[4], Frank[5], Grayson and Bradley[6], Hampton[7], Michel, Coleman and Kirby[8], Rausch, Grable and Musser[10], Rosecan, Baumgarten and Charles[11], Saslaw, Prior and Wiseman[12], and Wesselhoeft and Pearson[16]). One case has been reported from Australia (Southcott[13]). Four of these patients died and necropsy findings were described.

The basic clinical pattern of the disease is that of varicella with signs of pneumonic involvement. These include dyspnea, varying degrees of cyanosis and cough, frequently productive of bloody sputum, developing from the second to the sixth day after the onset of the exanthem. The patient usually recovers in from 2 to 7 days but the course may be rapid and progressive and terminate fatally. Diminution in pulmonary signs and symptoms generally coincides with subsidence of the rash. Complications are not infrequent; there may be concomitant involvement of other viscera by varicella virus; less commonly, secondary infection or thrombophlebitis has been observed. Treatment has been only supportive. Antibiotics have been used in most cases, but there has been no evidence that the illness was modified other than by protection against secondary bacterial infections. Pathological findings present features like those of other viral pneumonias. Type A inclusion bodies of varicella have been seen in 2 of 4 reported necropsy cases.

*The material in this paper was presented in part at the May, 1956, meeting of the Association of American Physicians at Atlantic City, N. J.

During the past 5 years at least 11 additional cases of varicella have been recognized in the Denver, Colorado, area in which there was clinical and roentgenographic evidence of pneumonia. In a twelfth case pneumonia was not clinically recognizable but the chest roentgenogram was consistent with the diagnosis.

Clinical Material. The patients in this series have been grouped according to the severity of the illness (Tables 1, 2, and 3).

GROUP I. In three instances (Cases 1, 2, 3) the disease was fulminant and fatal. Two patients died on the first day and the third on the third day after onset of respiratory symptoms. The early signs and symptoms of this group were not discernibly different from those of patients who survived a severe form of the illness (Group II). Adequate clinical data are not available on 2 of these 3 patients. Inasmuch as these 2 patients died before hospitalization, and the third after only a day and a half in the hospital, one can conclude that the disease may be extraordinarily rapid in its evolution. These 3 cases are briefly abstracted below including short necropsy summaries.

Case 1. E.F.A., a 35-year-old white adult male, was admitted to General Rose Memorial Hospital, Denver, Colorado, on June 26, 1951, dead on arrival. The patient had developed a mild systemic illness and a rash characteristic of chickenpox 4 days prior to death. His children had had typical chickenpox approximately 2 weeks previously. On the day before death he was seen by a private physician who stated that the patient was moderately ill with chickenpox but that there was no evidence of pneumonia. On the morning of his death the patient called his physician to say that he was more ill and had shortness of breath and cough. Immediate hospitalization was advised. The patient expired *en route* to the hospital. Postmortem examination was performed by Dr. Karl T. Neubuerger. The findings included: 1) Virus infection; Chickenpox (skin eruption in characteristic location). 2) Pneumonia, bronchial, hemorrhagic, widespread (virus type, varicella pneumonitis). 3) Lymphadenitis, mediastinal nodes, acute, moderate. 4) Myocarditis, acute interstitial, mild. 5) Hemorrhage, subendocardial and intramyocardial, left ventricle, recent. 6) Ulcers, stomach, fresh (multiple, shallow, hemorrhagic erosions). 7) Infiltration, fatty, liver, toxic, moderate. In the microscopic sections a few type A intranuclear inclusion bodies were found in desquamated alveolar septal cells. The interstitial tissue of the myocardium was more cellular than usual and in some fields the vascular endothelial cells were swollen. There were mild lymphocytic and polymorphonuclear infiltrations in the perivascular spaces, and some patches of recent hemorrhage.

Case 2. S.E.S., a 29-year-old white married male, was examined by the coroner's office of the City and County of Denver on January 29, 1953. The patient had developed a characteristic varicella eruption on January 25, 1953, accompanied by mild systemic reaction and a slight cough. His child had developed typical chickenpox on the same day. The patient was seen at home by his physician and given a sulfa preparation which he took during the remainder of his illness. He remained moderately ill at home until the evening of January 28, when he developed more cough and dyspnea. According to his wife, he became so short of breath in the middle of the night that he had to sit up in a chair in the living room. She found him dead in this position early in the morning of January 29, 1953. Postmortem examination was performed by Dr. William C. White. The findings included: 1) Cutaneous chickenpox. 2) Necrotizing and hemorrhagic pneumonitis characteristic of chickenpox pneumonia. 3) Pleural lesions compatible with visceral chickenpox. 4) Varicelliform lesions in the pharynx and esophagus. Type A inclusion bodies were found in the esophageal lesions.

Case 3. C.M.A., a 42-year-old white male clothing dry cleaner, was admitted to St. Luke's Hospital, Denver, Colorado, on November 23, 1955. His children had had chickenpox 2 weeks prior to the onset of his illness, which began November 19, 1955, with aching, generalized malaise and a typical varicella eruption on his abdomen and trunk. He was moderately ill for the next 2 days. On November 22, he developed a cough, hemoptysis, dyspnea, and cyanosis. He was sent to the hospital on the following day. Physical examination revealed a well-developed and well-nourished adult male in acute respiratory distress. There was a chickenpox rash on the trunk, chest, shoulders, face and extremities. Pulse was 84, respirations 20, blood pressure 110/85 mg. Hg and temperature 100° F. Physical findings included cyanosis and diffuse rales heard throughout both lung fields.

Laboratory findings: Hemoglobin 16.5 gm. %, leukocytes 8,550, polymorphonuclears 78%, lymphocytes 22%. Electrocardiogram revealed

TABLE 1.—CLINICAL FEATURES OF 12 PATIENTS WITH VARICELLA PNEUMONIA

Days of Fever after

TABLE 1.—CLINICAL FEATURES OF 12 PATIENTS WITH VARICELLA PNEUMONIA

Group	Patient No.	Patient Initials	Cyanosis	Hemoptysis	Maximum Temperature	Maximum Pulse	Maximum Respirations	Blood Pressure	Days of Fever after Onset of Pneumonia
	1.	EFA	?	?	?	?	?	?	?
I.	2.	SES	?	?	?	?	?	?	?
	3.	CMA	+	+	103°	134	48	110/85	2
	4.	WZ	+	+	105°	105	40	130/80	1
	5.	ES	+	0	104.9°	120	40	126/82	7
II.	6.	WAJ	+	+	104.6°	120	30	110/60	6
	7.	AS	+	0	102.0°	120	40	120/70	2
	8.	EY	+	0	101.3°	128	48	110/70	2
	9.	AEG	0	0	102.2°	125	36	136/80	2
III.	10.	GB	0	0	102.6°	112	20	108/64	3
	11.	VAM	0	+	103°	90	44	120/70	2
IV.	12.	JMW	0	0	103°	116	20	148/95	2

TABLE 2.—LABORATORY DATA AND COURSE OF 12 VARICELLA PNEUMONIA PATIENTS

Group	Patient Number	WBC	Sputum Culture	Blood Culture	Chemotherapy*	Days from Onset of Rash to Pneumonia	Roentgen Residual Beyond 3 Weeks	Complications
	1.	Not done	Not done	Not done	None	3–4	0	Died 1st day of pneumonia
I.	2.	Not done	Not done	Not done	Sulfa drug	4	0	Died 2nd day of pneumonia
	3.	8550	Not reported	Not done	Pen., Tet.	3	0	Died 4th day of pneumonia
	4.	9750	Non hem. strep. *N. catarrhalis*	Not done	Pen.	3	0	None
	5.	7400	D. Pn., Neiss & Strep.	Neg. × 4	Pen., Ery.	2	+	None
II.	6.	7600	No pathogens	Not done	Pen., Tet., Ery.			None
	7.	30000	No sputum	Neg.	Pen., Tet., Cortisone	2		Threatened abortion
	8.	8000	No sputum	Neg.	Pen., Sm.	2		None
	9.	6200	Not reported	Not done	Gantrisin, Pen., Oxy.	3	+	None
III.	10.	11000	*N. cat., B. hem.* Strep. (few)	Neg.	Oxy., Pen.	2	+	None
	11.	8100	None	Not done	Pen.	4	0	None
IV.	12.	12200	No sputum	Not done	None	1	0	None

* Pen. = Penicillin, Tet. = Tetracycline, Ery. = Erythromycin, Sm. = Streptomycin, Oxy. = Oxytetracycline

a sinus tachycardia with clockwise rotation. Roentgenogram showed a diffuse patchy infiltrate throughout both lung fields.

Course in the hospital: The patient's respiratory symptoms and cyanosis increased and he was thought to have heart failure. He was given oxygen, morphine, digitalis, tetracycline and penicillin. However, his course was progressively downhill and he expired on November 25, 1955. Postmortem examination was performed by Dr. William Millett. The findings included: 1) Chickenpox, cutaneous and visceral. 2) Pneumonitis, necrotizing, virus type, compatible with varicella pneumonitis. There were small necrotizing lesions in the liver, kidney and spleen. Type A inclusion bodies were seen in microscopic sections of the cutaneous and hepatic lesions.

GROUP II. In five cases (4, 5, 6, 7, 8) the illness was very severe but did not terminate fatally. These patients appeared critically ill at the time of admission to the hospital. There was unequivocal evidence of pneumonia, including dyspnea, cyanosis, frequently hemoptysis, and dullness to percussion, coarseness of breath sounds, and rales in varying degree. The chest roentgenograms of all showed a striking, diffuse, patchy nodular infiltrate throughout both lung fields. These patients remained severely ill for from 1 to 5 days after onset but all showed considerable improvement within 72 hours of hospitalization. Treatment included general supportive measures, oxygen and prophylactic antibiotics. One patient (Case 10) received hydrocortisone as an adjunct. Two cases from this group are abstracted below.

Case 5. E.S., a 35-year-old white male was admitted to Denver General Hospital October 3, 1955, complaining of aching in the back joints of 3½ weeks' duration. He had had some nausea and anorexia and a 10-pound-weight loss during the present illness. He had previous history of peptic ulcer. Physical examination revealed a well-developed, somewhat thin adult in no acute distress; temperature 37.6° C., pulse 132, respirations 20, blood pressure 126/82 mm. Hg. The remainder of the examination was unremarkable except for sinus tachycardia, clubbing of the fingers and toes, and pain in the knees, shoulder, fingers and toes.

Laboratory findings: Hemoglobin 17.1 gm. %, erythrocyte sedimentation rate 46 mm. per hour, leukocytes 9,900, polymorphonuclears 87%, lymphocytes 10%, monocytes 3%. Urinalysis showed a trace of albumin, but was otherwise within normal.

Course in the hospital. The patient developed a blowing apical systolic murmur on his third hospital day. Extensive serological and bacteriological studies failed to reveal any specific diagnosis. Chest roentgenograms showed clear lung fields. The working diagnoses were: 1) Possible rheumatic fever; 2) Possible collagen disease, type undetermined; 3) Hypertrophic pulmonary osteoarthropathy, etiology undetermined. During the second week of November, 1955, the patient was in a bed next to that of a patient who had

TABLE 3.—EPIDEMIOLOGIC DATA IN 12 PATIENTS WITH VARICELLA PNEUMONIA

Group	*Patient Number*	*Age*	*Sex*	*Date of Onset of Illness (Chickenpox)*	*Exposure*
	1.	35	M	6-22-51	Own children
I.	2.	29	M	1-25-53	Not known: child developed chickenpox same day
	3.	42	M	11-19-55	Own children
	4.	25	F	11-28-53	Own child
	5.	35	M	11-23-55	Patient with herpes zoster
II.	6.	38	M	3- 8-56	Own children*
	7.	25	F	3-28-56	Own child
	8.	28	F	4- 6-56	Own child
	9.	40	M	4- 1-53	Child on airplane
III.	10.	32	M	11-28-53	Own child
	11.	61	M	2- 1-56	Not known*
IV.	12.	36	M	3- 1-56	Not known (R.R. Dining car waiter)

* Patient's past history included chickenpox in childhood

herpes zoster. On November 23, 1955, the patient rather precipitously developed fever and a maculopapular and vesicular rash beginning on the trunk and abdomen and progressing peripherally (Fig. 1). Two days later the patient developed dyspnea and cough productive of copious amounts of sticky, brown sputum. Temperature was 101.9° F., pulse 120, and respirations 40. Temperature subsequently rose to 104.9° F. Medium and fine rales were present throughout the chest. Sputum cultures for pathogenic organisms included fungi and tubercle bacilli were negative. Blood cultures were negative. Coagulase negative staphylococci were cultured from the cutaneous lesions. Roentgenograms of the chest on November 25, 1955, revealed a diffuse patchy infiltrate throughout both lung fields (Fig. 2). At this time, the patient's leukocyte count was 7,400; polymorphonuclears 62%, lymphocytes 35%, monocytes 3%. He was given aqueous penicillin 1,000,000 units every 4 hours and erythromycin 0.25 gm. every 6 hours. After 3 days of acute illness the patient's temperature and symptoms subsided and the findings in the chest disappeared. However, roentgenograms of the chest showed considerable residual diffuse and nodular infiltrations in both lung fields. A surgical lung biopsy made on December 28, 1955, revealed only a mild amount of fibrosis. The patient was given salicylates for symptomatic control of his underlying illness. Two months after his acute pneumonia he still had diffuse nodular infiltrates throughout both lung fields.

Case 7. A.S., a 25-year-old white married female, three months pregnant, was admitted to Denver General Hospital, March 31, 1956. The patient noted the onset of a relatively mild systemic illness accompanied by a typical chickenpox eruption on March 28 (Fig. 3). Two days later, on March 30, she noted the onset of dyspnea and slight cough. During the next 24 hours her dyspnea became markedly increased and she was sent to Denver General Hospital. Her private physician had given her tetracycline at home. The patient's daughter had had chickenpox 2 weeks before the onset of her own illness. Physical examination revealed an acutely ill adult female in severe respiratory distress, using accessory muscles to breathe and deeply cyanotic when not receiving oxygen. She had a nonproductive

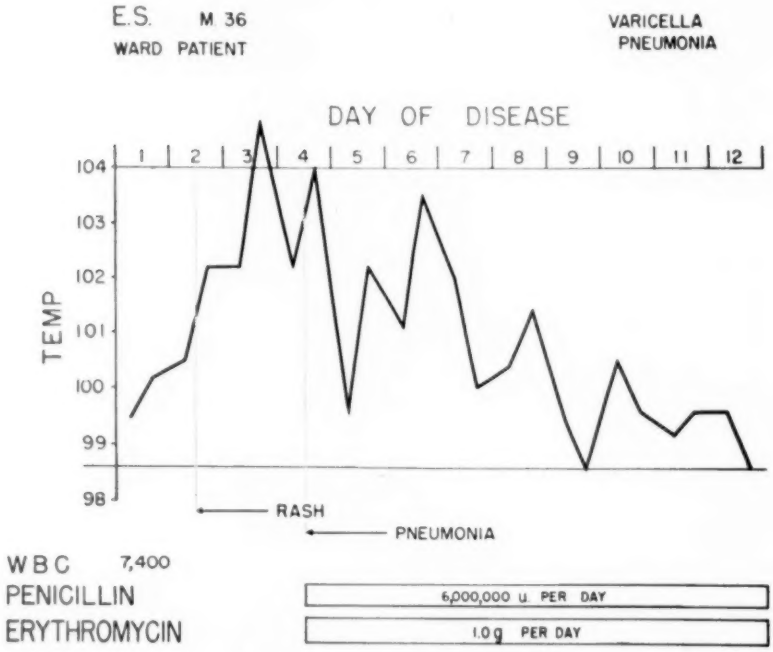


Fig. 1.—Clinical features of patient, E.S. (Case 5).

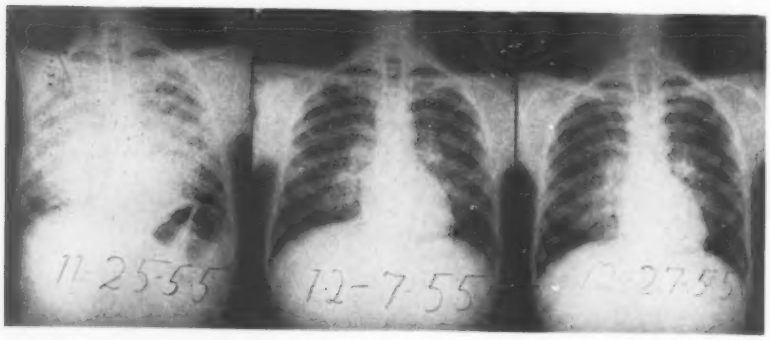


Fig. 2.—Chest roentgenograms of patient, E.S. (Case 5) taken on 3rd, 15th and 35th days after onset.

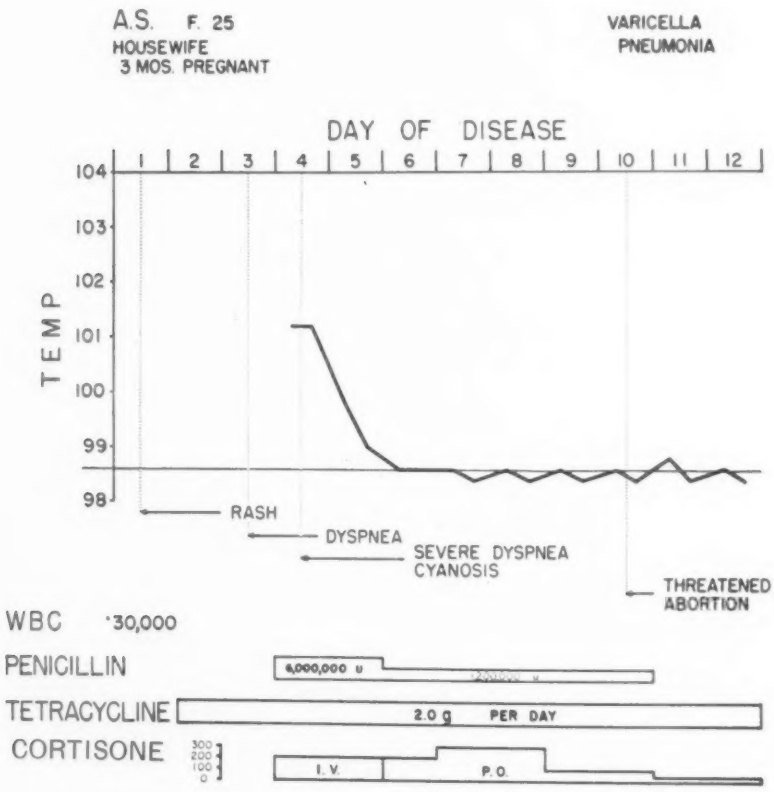


Fig. 3.—Clinical features of patient, A.S. (Case 7).

intermittent cough. Temperature 102° F., pulse 120, respirations 40, and blood pressure 120/70 mm. Hg. There was a vesicular and macular rash over the trunk, abdomen, face and back. Lesions were present though sparse on the extremities. There were diffuse rales throughout both lung fields and the breath sounds were harsh.

Laboratory findings: Leukocytes, 30,000, polymorphonuclears 71%, lymphocytes 29%. Sputum could not be obtained for culture. Blood cultures were negative. The cold agglutination test was negative on the third and tenth hospital day. Chest roentgenogram showed a diffuse, mottled, nodular, miliary, and patchy infiltrate throughout both lung fields (Fig. 4). The patient was given oxygen, tetracycline, and penicillin. She was critically ill during the first 24 hours of her hospitalization and intravenous hydrocortisone was added to the regimen. This was changed to oral cortisone by the third day. The patient's temperature returned to normal by the second hospital day. Her dyspnea improved considerably although she was still cyanotic when not taking oxygen for the first 3 days in the hospital. During these first and second days in the hospital the patient had rather severe lower abdominal cramps. On her seventh day she developed vaginal bleeding and threatened to abort. Also, on the seventh day the patient developed a sharp left posterior chest pain which radiated to the left scapula and left arm and was made worse by deep breathing or cough. Auscultation at this time revealed a sharp, scratchy friction sound at the end of inspiration in a small area in the left posterior axillary line. The patient had no hemoptysis and no signs of thrombophlebitis. Chest roentgenogram showed clearing of her pneumonia with no evidence of pulmonary infarct or pleural reaction. She was thought to have a pleurisy in association with her varicella pneumonia rather than a pulmonary infarct or other cause for pleurisy. The pleuritic pain and friction disappeared within 48 hours. Her subsequent convalescence was uneventful until the sixth week. At that time she was admitted to another hospital where a 4-month macerated fetus was aborted.

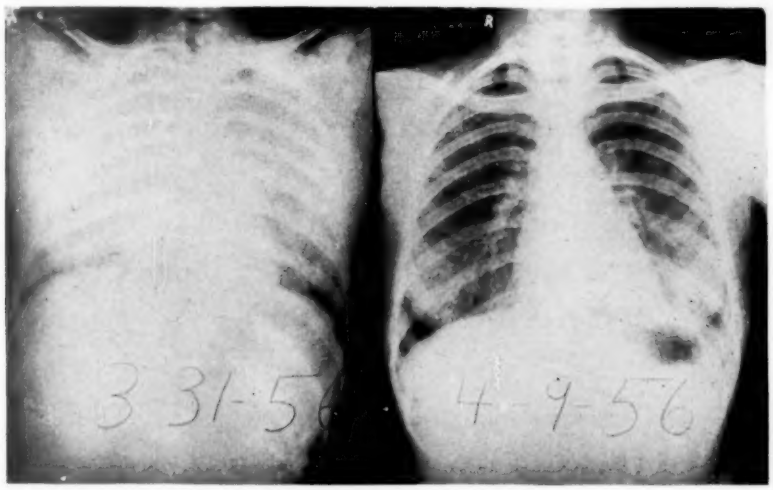


Fig. 4.—Chest roentgenograms of patient, A.S. (Case 7) taken on 4th and 13th days after onset.

GROUP III. Three patients (Cases 9, 10, 11) were less critically ill than the patients in Group II. They were not described as cyanotic. The chest roentgenograms showed somewhat less extensive involvement. They became afebrile and convalescent within 3 days of admission. The course of one of these (Case 9) is outlined below.

Case 9. A.E.G., a 40-year-old white airlines pilot was admitted to Colorado General Hospital on April 4, 1953. He had noted generalized aching, fever, intermittent chills, and mild nausea for 5 days prior to admission. Three days before admission he developed a papular and vesicular rash which became pustular and crusted, beginning on the abdo-

men and trunk and spreading to the shoulders. On the day of admission he noted severe dyspnea and cough. Two weeks before the onset of this illness he had carried an infant sick with fever and rash onto an airplane. There was no past history of chickenpox. Physical examination revealed a well developed and well nourished adult male, in moderate respiratory distress; pulse 88, respirations 36, blood pressure 136/80 mm. Hg, temperature 102.2° F. There was a varicella eruption over the trunk and shoulders. There were fine inspiratory rales in both lung fields. Physical findings were otherwise not remarkable.

Laboratory findings: Hemoglobin 15.9 gm. %, leukocytes, 6,200, polymorphonuclears 58%, lymphocytes 40%, eosinophils 2%. Electrocardiogram showed flattened T waves in leads 1, 2, 3, and AVL. Roentgenograms of the chest revealed patchy infiltrations throughout both lung fields (Fig. 5).

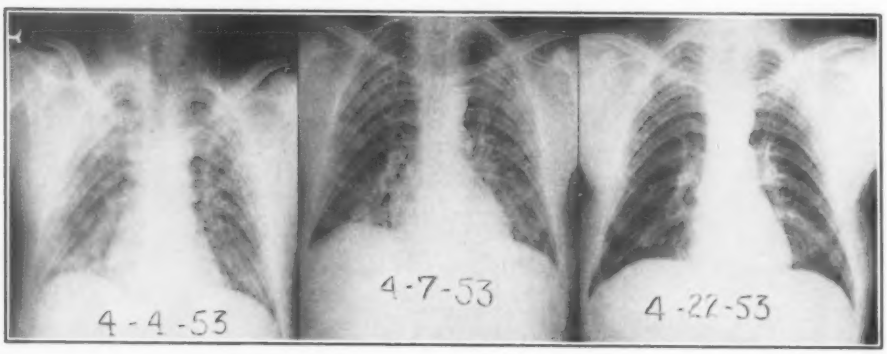


Fig. 5.—Chest roentgenograms of patient, A.E.G. (Case 9) taken on 4th, 7th and 22nd days after onset.

Course in the hospital. The patient was treated with aspirin and procaine penicillin 1,000,000 units b.i.d. He became afebrile within 24 hours. There was marked improvement of respiratory symptoms. The patient was discharged to another hospital on the third hospital day much improved and had an uneventful convalescence. Subsequent chest films showed a diminishing but persistent infiltrate for several weeks.

GROUP IV. One patient had moderately severe cutaneous chickenpox with fever and subjective malaise. There was no clinical evidence of significant pneumonial involvement. However, the chest roentgenogram showed a definite but relatively faint diffuse, patchy infiltrate similar to those of the more severely ill patients (Case 12).

Case 12. J.M.W., a 36-year-old colored male railroad dining-car waiter, entered Denver General Hospital on March 3, 1956. Two days before admission the patient developed malaise, headache, fever and chilliness. On the day before admission, he noted the onset of a macular and vesicular rash on his trunk, neck and arms. He saw a physician who made the diagnosis of chickenpox. The patient had never had chickenpox. He had had no known recent contact with chickenpox. His past history and systems review were noncontributory. Physical examination revealed a well developed and well nourished colored male in no acute distress; temperature 103° F., pulse 116, respirations 20, blood pressure 148/93 mm. Hg. There was a maculopapular vesicular rash over the trunk, arms and face. Chest was clear to auscultation and percussion. Physical findings were otherwise within normal limits.

Laboratory findings: Hemoglobin 15.9 gm. %, leukocytes 12,200, polymorphonuclears 48%, lymphocytes 50%, monocytes 2%. Some atypical lymphocytes were seen. Serology was negative. Roentgenogram of the chest showed definite diffuse but faint, soft, patchy, mottled and nodular infiltrates (Fig. 6).

Course in the hospital. The patient was asymptomatic except for some pruritus. His temperature was normal by the third hospital day. On one occasion a few rales were heard at the right posterior lung base. These disappeared after coughing. Roentgenogram of his chest showed marked clearing by his third hospital day. The patient received no anti-

biotic therapy and was discharged essentially well on March 10, 1956.

Discussion. The cases of varicella pneumonia reported in this series occurred predominantly in young adults and were usually contracted through exposure to children with varicella, most often the patient's own. With one exception (age 61) patients' ages ranged from 25 to 42 years in the present group. This distribution is similar to that of previously reported cases, in which ages ranged from 20 to 46 in all but one patient, who was 71. It is interesting that 2 patients in the present group gave a history of having previously had chickenpox.

The patients have been divided into 4 groups in order to illustrate the wide variation in the extent and clinical severity of chickenpox pneumonia. The pneumonia may be massive and fulminant (Group I) and progress rapidly to a fatal outcome. It may be extensive and severe with the patient in critical condition over a period of a few days (Group II). It may be moderately severe with both clinical and roentgenographic manifestations of pneumonia less extensive than in Groups I or II (Group III), and finally, the pneumonia may be subclinical and diagnosed only if a roentgenogram is made at the right time (Group IV).

The actual incidence of pneumonia as a specific complication of chickenpox is difficult to determine. In a study of 2,534 patients of mixed ages who had chickenpox Bullowa and Wishik[1] found only 21 with complicating pneumonia,

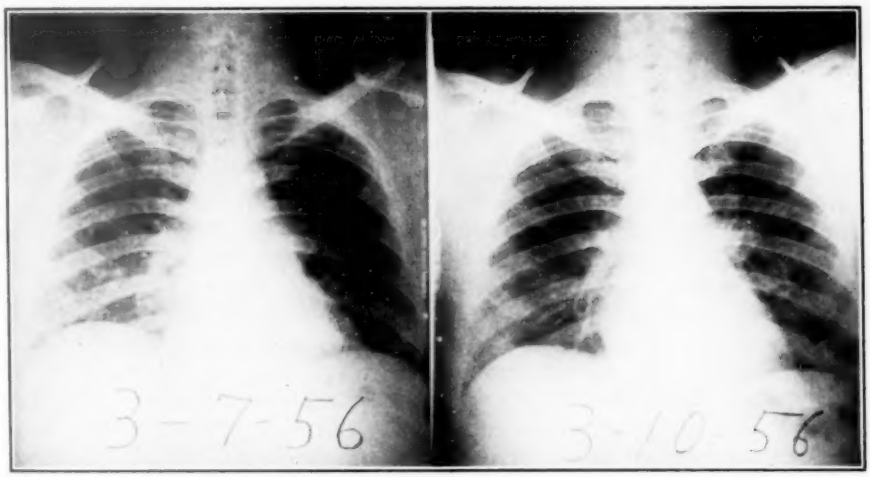


Fig. 6.—Chest roentgenograms of patient, J.M.W. (Case 12) taken on 7th and 10th days after onset.

and in these patients the pneumonia was thought to be due to secondary bacterial infection, usually streptococcal. Waring, Geever and Neubuerger[15] were the first to ascribe a specific viral etiology to pneumonia complicating chickenpox. Relatively few cases have been reported since that time. That 12 cases have appeared in one city in a 5-year period, 6 of them within 6 months, suggests that this complication is at times much more common than the surprisingly small number of cases recorded in the literature indicates. It

is probable that pneumonia would have been recognized more often if chest roentgenograms had been taken routinely on all patients with varicella. This has been avoided in many hospitals unless there has been obvious clinical indication.

Pleuritic pain has not been a common clinical feature of chickenpox pneumonia. One patient in the present group (Case 7) complained of pleuritic chest pain and a pleural friction rub was heard. Involvement of the pleura was present at necropsy in another patient (Case 2). Of previously reported cases, two had shown clinical evidence of pleural involvement and an additional patient who had been necropsied was shown to have involvement of the pleura.

With this wide potential variation in the clinical manifestations of the illness it is difficult to evaluate therapy. Most patients have received antibiotic therapy in addition to supportive measures. Aqueous penicillin in combination with erythromycin or a tetracycline drug was used in the recent severe cases on the assumption that streptococcus, pneumococcus or staphylococcus might play a significant role as a secondary invader. It is possible that the antibiotics used may have aided in the recovery of some patients. There is no substantial evidence that chemotherapy specifically affects the course of varicella infection. The role which cortisone may have played in the therapy of Case 7 of the present series is speculative. This patient was desperately ill at the time of admission. Intravenous hydrocortisone was administered together with high doses of penicillin and tetracycline. The patient's temperature fell rapidly to normal within 24 hours after the institution of treatment and remained within normal limits thereafter. However, though improved, she continued to be dyspneic and cyanotic for the next 3 days when not receiving oxygen.

One patient (Case 5) acquired his illness in the hospital. The only known contact was another patient in the next bed on an open ward who had herpes zoster. The clinical association of herpes zoster and chickenpox is well known and the viruses are indistinguishable in the laboratory[9]. Whether this patient should be considered to have had pneumonia complicating generalized herpes zoster or complicating chickenpox is a semantic problem. His clinical illness matched that shown by other patients with chickenpox pneumonia. A surgical lung biopsy taken 5 weeks after his acute pneumonia failed to cast light either on his undiagnosed underlying systemic illness or on the nature of the residual infiltrate still present at the time of his chest roentgenogram. Examination of microscopic sections revealed only a minor amount of nonspecific fibrosis.

In 4 of the 8 surviving patients of the present group a diffuse nodular infiltration persisted in the chest roentgenogram for 3 weeks or more beyond the acute illness. In one patient (Case 5) the infiltration was present for at least 3 months. Similar delay in clearing of the chest film was noted in several of the previously reported cases. How long the infiltration may persist is not known. Long-term follow-up of such patients, both in regard to roentgenographic features and pulmonary function, should be of interest.

The diagnosis of varicella in the cases reported above was based entirely on clinical and epidemiological evidence. No attempts were made to isolate varicella virus or to demonstrate increases in antibody to varicella virus. Type A inclusion bodies were demonstrated in the tissues of each of the 3 necropsied patients. These may be regarded as inclusions specific for the

varicella-herpes zoster virus[14]. The differentiation of severe varicella pneumonia from variola becomes increasingly difficult as a new generation of physicians takes over which has had little or no direct contact with variola. In one instance (Case 8) considerable confusion resulted when a consultant proposed the diagnosis of smallpox. Seventy contacts were vaccinated. The situation was clarified by the failure to isolate variola virus from vesicular lesions and the failure of the patient to develop variola antibody*. In addition, two nurses who had been exposed to the patient obligingly developed characteristic varicella 14 and 16 days later.

Summary. 1. Data have been presented on 12 patients with varicella pneumonia, 3 with fatal outcome, observed during the past 5 years.

2. The severe and not infrequently lethal nature of this complication has been stressed.

3. Questions have been raised about the true incidence of pulmonary involvement in adults who have varicella.

*These studies were carried out through the courtesy of Dr. J. E. Smadel, Director, Communicable Disease Division, Walter Reed Army Institute of Research.

REFERENCES

1. **Bullowa, J. G. M.,** and **Wishik, S. M.:** A.M.A. Am. J. Dis. Child., **49,** 923, 1935.
2. **Bunn, P. A.,** and **Hammond, J. D.:** New York J. Med., **50,** 1485, 1950.
3. **Claudy, W. D.:** A.M.A. Arch. Int. Med., **80,** 185, 1947.
4. **Eisenbud, M.:** Am. J. Med., **12,** 740, 1952.
5. **Frank, L.:** A.M.A. Arch. Path., **50,** 450, 1950.
6. **Grayson, C. E.,** and **Bradley, E. J.:** J. Am. Med. Assn., **134,** 1237, 1947.
7. **Hampton, A. G.:** A.M.A. Arch. Int. Med., **95,** 137, 1955.
8. **Michel, J. C., Coleman, D. H.,** and **Kirby, W. M. M.:** Am. Pract. & Digest Treat., **2,** 57, 1951.
9. **Rake, G., Blank, H., Coriell, L. L., Nagler, F. P. O.,** and **Scott, T. F.:** J. Bact., **56,** 293, 1948.
10. **Rausch, L. E., Grable, T. J.,** and **Musser, J. H.:** New Orleans Med. & Surg. J., **96,** 271, 1943.
11. **Rosecan, M., Baumgarten, W., Jr.,** and **Charles B. H.:** Ann. Int. Med., **38,** 830, 1953.
12. **Saslaw, S., Prior, J. A.,** and **Wiseman, B. K.:** A.M.A. Arch. Int. Med., **91,** 35, 1953.
13. **Southcott, R. V.:** Med. J. Australia, **40,** 717, 1953.
14. **Stokes, J. E.:** Viral and Rickettsial Infections of Man. Edited by **T. M. Rivers.** Philadelphia: J. B. Lippincott Co., 1952, p. 508.
15. **Waring, J. J., Neubuerger, K. T.,** and **Geever, E. F.:** A.M.A. Arch. Int. Med., **69,** 384, 1942.
16. **Wesselhoeft, C.,** and **Pearson, C. M.:** New England J. Med., **242,** 651, 1950.

SUMMARIO IN INTERLINGUA

Pneumonia a Varicella in Adultos

1. Es presentate datos relative a 12 patientes con pneumonia a varicella, observate in le curso de 5 annos. In 3 del casos le termination esseva mortal.

2. Es sublineate le sever e non infrequentemente letal character de iste complication.

3. Es sublevate questiones relative al ver incidentia del implication pulmonar in adultos qui ha varicella.

ERYTHROMYCIN:* AN EVALUATION FOR CLINICAL TOXICITY

By Mark J. Ciccantelli, M.D.
CLINICAL INSTRUCTOR OF MEDICINE

AND

Mark W. Garry, M.D.
ASSOCIATE PROFESSOR OF MEDICINE

(From the Department of Medicine, Veterans Administration Hospital, Wood, Wisconsin, and Marquette University School of Medicine, Milwaukee, Wisconsin)

Erythromycin, which was introduced for clinical use early in 1952 (Haight and Finland[3], Heilman *et al.*[4], and McGuire *et al.*[6]), was originally derived from a sample of soil collected in the Philippine Islands. The microörganism responsible for the production of the active principle was a strain of *Streptomyces erythreus.* The chemical structure, although not definitely determined, is thought to be C–3,9, H–7,3, NO–1,3; no benzol ring is contained in the formula. In its final form, the drug appears as a white crystalline compound only slightly soluble in water.

While it is not a "broad-spectrum" antibiotic, the range of this agent's efficacy is sufficient to make it comparable to penicillin (Haight[2]). The initial reports dealing with the use of erythromycin indicate that it exerts its effects chiefly against the Gram-positive organisms (Kirby, Forland and Maple[5], Shoemaker and Yow[7], and Wise and Spink[8]). These studies were based on *in vitro* observations, later confirmed by clinical trial. Its antimicrobial action was found to vary in potency from bacteriostatic to bacteriocidal, according to the sensitivity of the organism and the concentration of the drug. Although the drug is quite effective when given orally, it may be administered parenterally (Geraci *et al.*[1]) when high initial tissue concentrations are desired.

As a result of our preliminary investigation of the drug in 1952–1953 and the reported experiences of others[1-8] which suggested the clinical value of erythromycin, it was decided to extend the study to include an additional 75 patients and observe specifically for toxicity of the antibiotic. As originally planned, the purpose of the study was an evaluation of such effects as change in blood picture, derangement of liver function, renal irritation, sensitivity reactions, and gastrointestinal intolerance. Appropriate laboratory examinations designed to detect such toxicity were contemplated on a pre- and post-therapy schedule. Since it was our primary aim to discover these limitations of the drug rather than its antibacterial efficacy, no attempt was made to restrict its use to the treatment of specified infectious states or organisms. This resulted in use of the drug in a diverse variety of conditions and circumstances. Although satisfactory clinical observation of the patient was obtained in every instance, the limitations imposed by short-term hospitalization, inadequate follow-up or incom-

*The erythromycin (Ilotycin) used was kindly supplied by Eli Lilly and Company, Indianapolis, Indiana.

plete data frustrated the ambitious intentions originally conceived. It is our feeling however, that in one major respect, that of gastrointestinal tolerance, a clear estimation was possible from the available information. A very significant over-all impression in other directions is also noteworthy. We are accordingly submitting these observations with such reservations in mind.

Material and Methods. 1. MATERIAL. The initial 26 cases were supplemented by 54 others, totalling 80, considered as suitably observed. These patients were all hospitalized male veterans ranging between the 3rd and 7th decades of life. Most of the patients were in the age group between 35 and 60 years of age. The period of study began in January, 1953, and was terminated in June, 1954, at which time 100 cases had been accumulated. Twenty cases either failed to have adequate observation or were lost to further study.

2. DISEASE ENTITIES TREATED. These included almost all of the commonly encountered infections seen in general hospital practice. Every major organ system involvement was represented as seen by the numerical analysis of the case material:

a) Respiratory (including bacterial pneumonia, chronic bronchopulmonary infections of the asthma-emphysema-bronchitis type, ornithosis, pleural effusion, mediastinitis, sinusitis)	34
b) Genitourinary tract infections (pyelonephritis, cystitis, urethritis, epididymitis)	8
c) Dermatologic (atopic eczema, erysipelas, cellulitis, carbunculosis, postoperative wound infections, decubitus, cysts)	12
d) Bacteremia (cause not specified)	1
e) Cardiovascular diseases (including bacterial endocarditis, rheumatic carditis, pericarditis)	3
f) Musculoskeletal (infectious arthritis, Reiter's syndrome)	3
g) Gastrointestinal (enterocolitis, peritonitis, localized intraabdominal abscess)	5
h) Fever of undetermined origin and febrile central nervous system disease	2
i) Prophylactic administration in minor (postoperative) procedures, during course of ACTH therapy, debilitated states	12

3. BACTERIOLOGIC ASPECTS. Identification of the specific organism was attempted, wherever possible, prior to initiation of therapy. The spectrum of responsible agents was as follows: *H. Staph. aureus*, 22 instances singly, 6 instances as part of a mixed flora; Pneumococci, 10 instances singly, 2 instances in combination with another organism; B hemolytic Streptococcus (enteric and other variants), 15 instances, either alone or with associated organisms; Aerobacter-Pseudomonas, 3; Proteus Group: Ornithosis (C.F. titer diagnostic) 1; Gonococcus, 1. Situations such as idiopathic pericarditis, "sterile" pleural effusion, atypical pneumonia, and others, were left unsettled bacteriologically.

4. DURATION OF THERAPY AND DOSAGE. The duration of treatment ranged from 1 to 40 days. Over one-half of all the patients received the drug for a period of between 7 and 15 days. Twenty were treated for less than one week; the remainder received the drug for more than 15 days: 20 cases 1 to 6 days, 44 cases 7 to 15 days, 17 cases 16 to 40 days. Dosage was planned according to the therapeutic indication. In most infectious states an initial "priming" of 500 mg. was followed by maintenance levels of 300 to 400 mg. administered at 6 hourly intervals. In such conditions as postoperative prophylaxis, or in conjunction with ACTH or cortisone therapy, a schedule of 200 mg. q.i.d. was adopted. The treatment schedules fell into four groups as follows: 0.8 gm./24 hrs., 13 cases; 1.2 gm./24 hrs., 19 cases; 1.6 gm./24 hrs., 42 cases; and 1.6 up to 2.0 gm./24 hrs., 7 cases. Thus in 61 cases the dosage varied between 1.2 and 1.6 gm., and in 68, more than 1.0 gm. per day was administered. The drug was prescribed orally in all but two instances, being used intravenously in two desperately ill patients.

Results. TOXIC MANIFESTATIONS. These will be considered in categoric fashion.

a) *Drug fever*: no cases with this complication were observed.

b) *Sensitivity reactions*, such as skin eruptions, asthma, pruritus, and the like, were not encountered.

c) *Parenchymal damage*, specifically hemopoietic, renal and hepatic derangement, were sought for clinically in all instances in terms of sore throat, hematuria, jaundice, purpura, gingivitis, neuropathy, and others. These symptoms were never reported in the entire series. Evidence of deleterious effect in the peripheral hemogram or

routine urinalysis was lacking in 72 cases where these studies were performed during and after therapy. Thirteen cases had preliminary liver function studies prior to therapy and repeat evaluations upon completion. None of these demonstrated any deterioration, despite the fact that several patients were known to have parenchymal damage of a cirrhotic type. In all instances, liver function remained stable or improved while under our observation.

d) *Gastrointestinal Side-effects.* Under this heading are grouped such symptoms as nausea, emesis, cramping abdominal discomfort, diarrhea or other stool change, proctitis, pruritus ani, "heartburn," and others. In the entire series, 12 instances of such symptoms occurred. These consisted of 2 cases of abdominal pain or cramps, 2 cases of abdominal discomfort and loose stools, and 8 cases in which diarrhea alone was reported. Careful analysis of the circumstances surrounding each such case revealed that one case of abdominal distress occurred in a patient with gastric carcinoma; in three others, Ilotycin was being given in combination with another drug (for example, Apresoline, digitalis and oxytetracycline), in another, "cramps" appeared only on the first of 10 days of treatment, and in one other case the patient's diarrhea developed in the course of a small outbreak of enteritis which afflicted several others on the ward not receiving any form of antibiotic. This reduced to six the number of cases in which gastrointestinal symptoms could reasonably be attributed to the drug alone. Of these, only one developed sufficient discomfort to necessitate discontinuation of the drug, and symptoms subsided in short order (36 hours) thereafter. Another patient's diarrhea developed within a 3-day period after treatment had been stopped, but the patient had only moderate discomfort which cleared in a few days. No prolonged diarrhea was reported, nor was pruritus ani complained of during the hospitalization period, which in most of the cases extended well beyond cessation of drug therapy.

Recapitulation of this aspect of the study reveals 6 instances of gastrointestinal derangement, manifested by mild to moderate diarrhea alone in 4, and diarrhea associated with abdominal distress in 2 others. This makes an overall incidence of 7.4% in what is admittedly a small series. Only in one case was this complication considered of such magnitude as to curtail therapy, and there were no diarrheas of longer than 3 days' duration. Unfortunately, no stool cultures were obtained in these situations, hence nothing can be surmised as to etiology. Although a not inconsequential figure in terms of frequency, the significance of this symptom is minimized to considerable degree by its comparatively innocuous nature. There is ample basis, therefore, to state that where its use appears indicated, the consideration of potential gastrointestinal toxicity is not a deterrent to erythromycin therapy.

Summary. 1. Erythromycin was employed in a variety of disease states involving a total of 80 patients.

2. The drug has established itself as a definite adjuvant to the management of surgical and medical infections, although this aspect was not our primary concern.

3. The evaluation of over-all toxicity, when reviewed in terms of gastrointestinal tolerance, resulted in an incidence of diarrhea of 7.4%. None of these was serious in nature, and in only one case was discontinuation of the drug necessary.

4. There were no fatalities attributable to the drug, nor did we encounter sensitivity reactions, renal or hepatic damage.

REFERENCES

1. **Geraci, J. E., Martin, W. J., Nichols, D. R.,** and **Larson, L. W.:** Proc. Staff Meet., Mayo Clin., **29,** 536, 1954.
2. **Haight, T. H.:** J. Lab. & Clin. Med., **45,** 15, 1954.
3. **Haight, T. H.,** and **Finland, M.:** New England J. Med., **247,** 227, 1952.
4. **Heilman, F. R., Herrell, W. E., Wellman, W. E.,** and **Geraci, J. E.:** Proc. Staff Meet., Mayo Clin., **27,** 285, 1952.
5. **Kirby, W. M. M., Forland, T.,** and **Maple, F. M.:** A.M.A. Arch. Int. Med., **92,** 464, 1953.
6. **McGuire, J. M., Bunch, R. L., Anderson, R. C., Boaz, H. E., Flynn, E. H., Powell, H. M.,** and **Smith, J. W.:** Antibiotics & Chemother., **2,** 281, 1952.
7. **Shoemaker, E. H.,** and **Yow, E. M.:** A.M.A. Arch. Int. Med., **93,** 397, 1954.
8. **Wise, R. I.,** and **Spink, W. W.:** Bull. Univ. Minnesota Hosp., **24,** 645, 1953.

SUMMARIO IN INTERLINGUA

Erythromycina: Un Evalutation de su Toxicitate Clinic

1. Erythromycina esseva empleate in un varietate de statos morbic in un total de 80 patientes.

2. Le droga se ha establite como un adjuvante de valor in le tractamento de infectiones chirurgic e medical, ben que iste aspecto non esseva nostre prime interesse.

3. Le toleration gastrointestinal, studiate como parte del evalutation general del toxicitate, esseva manifestate in un frequentia de 7,4 pro cento de diarrhea. Nulle caso de diarrhea esseva grave, e in solo un caso esseva necessari le discontinuation del droga.

4. Il habeva nulle morte attribuibile al droga. Nos incontrava nulle reactiones de sensibilitate, ni damnos renal o hepatic.

THE DYNAMICS OF PLACEBO THERAPY: A CLINICAL STUDY

By H. Keith Fischer, M.D.
ASSISTANT PROFESSOR OF PSYCHIATRY

AND

Barney M. Dlin, M.D.
INSTRUCTOR IN PSYCHIATRY

(From the Departments of Psychiatry and Internal Medicine at Temple University Hospital and School of Medicine. Philadelphia, Pennsylvania)

Certainly no medication dates earlier in human history than the placebo. Placebo therapy is unique in its timeless potency and popularity, and the advent of specific drugs has not forced it into oblivion. Modern psychotherapy has not adequately explained it. Meanwhile, it has not achieved full scientific status, although all physicians, knowingly or unknowingly, employ it at times, know something about it in varying degrees, and privately talk of its accomplishments.

This paper records our answers to such questions as: What is the source of the placebo's potency? What are its dynamic actions? How is it related to therapy? What are its indications? What are its values?

Methods of Study. A series of 75 psychosomatic patients in a doubly controlled experiment served as a source for observations of placebo action. Those receiving pills were divided into two groups; one, Group A (28 patients) receiving a pharmacologically potent pill containing a sympathetic inhibitor, parasympathetic inhibitor, and a central nervous system sedative, while the other, Group B (24 patients) received a nonpotent (placebo) pill of identical appearance. The investigator also did not know which was the "potent" pill. In addition to the pills, both groups received psychotherapy. Theoretically, the pharmacologically potent pill should influence the distribution of the somatic symptoms which are a common concomitant of emotional conflict, while the placebo should have no such influence. A third group, Group O (23 patients), received only psychotherapy, no pills.

CASE SELECTION AND DIAGNOSIS. All patients came from the psychosomatic section of Temple University Hospital and the outpatient clinics of the Departments of Medicine and Psychiatry. The cases were consecutive and unselected except for diagnosis. In each instance an organic cause had been ruled out and in each it was considered that the somatic complaint was primarily functional in origin. Any patient who suffered from one or more of the following complaints was included in the study: a) gastrointestinal disturbances: nausea, vomiting, "indigestion," excessive constipation, and functional diarrhea; b) palpitations; c) dysmenorrhea; d) menopausal tension; e) headaches and migraine; f) anxiety state; g) acne and neurodermatitis; h) asthma (high functional factor); and i) rheumatism (psychogenic).

DATA. Information concerning the patients and data abstracted during the course of the study were recorded on three forms.

a) Form 1 was a summary of the past medical and psychological history. It also included history of present illness, pertinent summary of environmental and emotional data, physical examination and prognosis.

b) Forms 2a and 2b referred to treatment follow-up data. These were collected at weekly intervals over the course of 4 months. Form 2a consisted of information filled out by the patient, dealing with his subjective emotional feelings, his mental outlook, his performance, his physical complaints and an evaluation of the stresses and strains with which he had been faced. Form 2b was filled out by the physician, representing his own evaluation of the patients on the same subjects.

INSTRUCTIONS. Each patient was informed that the pills were given to alleviate his symptoms and that initially they were to be taken

three times a day after meals, and at bedtime if necessary. Each patient was told that, since studies had ruled out organic disease, the emotions would be investigated and treated. The patient was requested to fill in Form 2a prior to each visit so as to give an idea of "how he got along for the week." At the end of each therapeutic hour Form 2b was filled in by the therapist as a comparison. The patient was seen for one hour at a time in the same manner as any patient treated in brief psychoanalytic psychotherapy.

THE PSYCHIATRIC DIAGNOSIS. The standard nomenclature for mental diseases (set up by the American Psychiatric Association) was used to "fit" patients into categories for the purpose of statistics. The patients fell into three categories to indicate the severity of their psychiatric illnesses as shown in Table 1.

TABLE 1.—PSYCHIATRIC DIAGNOSIS

Group	*O*	*A*	*B*	*Total*
Psychotic	3	5	6	14
Severe Neurotic	17	20	14	51
Mild Neurotic	3	3	4	10
TOTAL	23	28	24	75

The psychotic patients were those who had frank delusions, hallucinations, and who had lost contact with reality. The mildly neurotic were those whose symptoms were mild, who made good reality adjustments, and who were not in any way incapacitated by their problems. The intermediate severely neurotic group was the largest.

These patients comprised practically all the diagnostic categories outlined by the new nomenclature. The psychiatric diagnosis was made by clinical observation only. Psychological tests were not given. In all cases the physical examination was carried out by the referring physician or some doctor other than the therapist.

The average number of patient-hours of psychotherapy per individual was 17.2 in Group O, 16 in Group A and 21.8 in Group B. The patients hospitalized on the psychosomatic service received the most intensive psychotherapy. The majority of the patients (62) were seen as outpatients, an average of once a week.

Table 2 reveals the source of patients.

Results. Evaluation of improvement was based on the subjective impression of the patient and the clinical judgment of the therapist. Improvement was "questionable" when doubt or disagreement occurred between the physician and the patient. Consideration was given both to somatic and to psychic symptoms. The results are graphically shown in Fig. 1.

Of the total 75 patients of the three groups, 36 (48%) showed improvement, 27 (36%) showed no improvement or were made worse, and 12 (16%) showed questionable improvement. It was not possible to differentiate between the placebo group and the "potent" pill group, each ("A" and "B") showing approximately the same percentage of improvement and "no" or "questionable" improvement. The "O" group showed the greatest percentage of improvement, but the Chi-square test reveals that there is no statistical difference in these three groups. The "B" group was somewhat more disturbed psychologically.

TABLE 2.—SOURCE OF PATIENTS

		Group		
Type of Patient	*Number*	*O*	*A*	*B*
Private (Total)	37	18	11	8
Clinic Outpatients	38	5	17	16
TOTAL	75	23	28	24

In Fig. 2 are presented the results according to the psychiatric classification of the severity of illness. The greatest percentage of improvement occurred in the "mild psychoneurotic" group, while the greatest percentage of "no" improvement was seen in the psychotic group of patients. The "questionably" improved patients were about constant in all three groups.

Chi-square analysis reveals that these three groups were more divergent than could be accounted for by

random sampling. Similar analysis of the neurotic groups reveals a statistically significant difference ($P<.02$). Comparison of the mild neurotic and psychotic groups reveals no statistical significance. This last result must be understood in the light of the small "psychotic" sample size.

The subjective reactions to the pills are summarized in Fig. 3 according to psychiatric diagnosis. Those who reacted favorably are called "positive

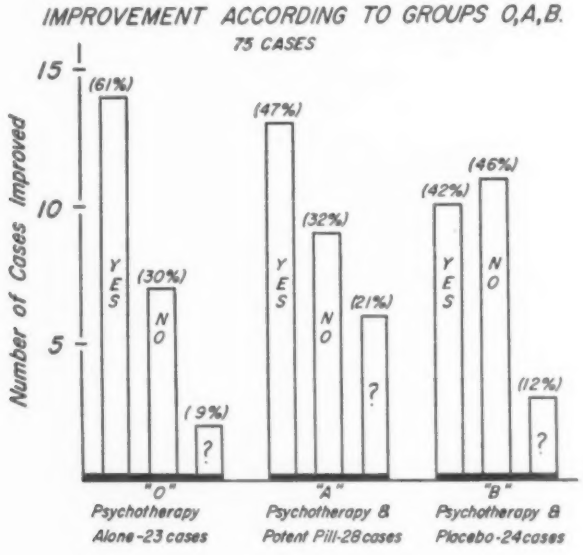


Fig. 1.

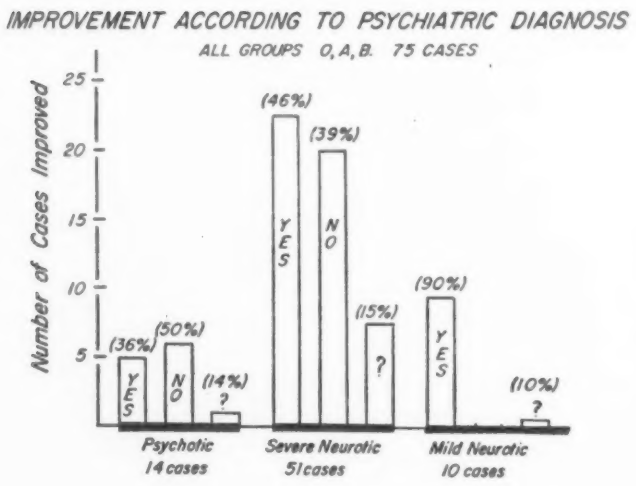


Fig. 2.

(+) reactors," while those who reacted unfavorably are "negative (—) reactors." Those who reacted questionably or had no reaction are identified appropriately.

The negative pill reactors exceeded the positive pill reactors in the psychotic group, while in the mild psychoneurotic group the positive pill reactors exceeded the negative pill reactors. The

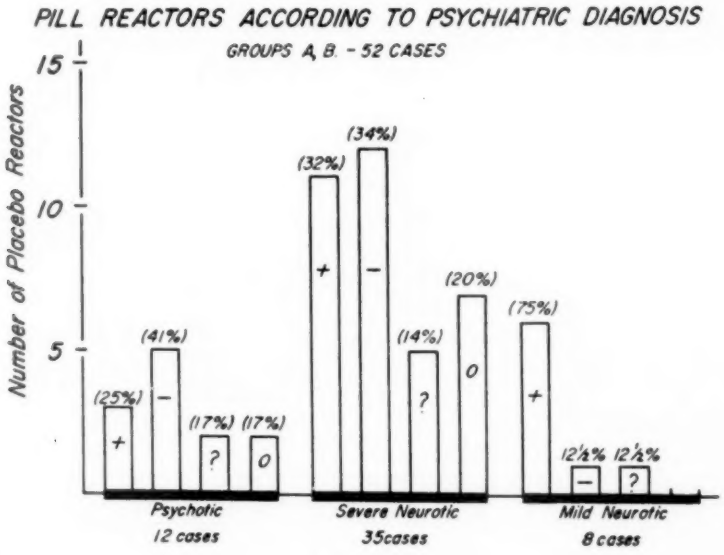


Fig. 3.

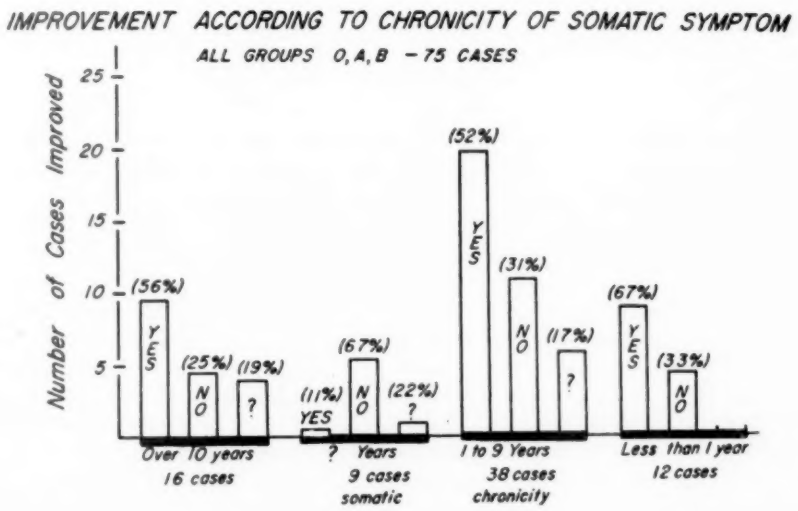


Fig. 4.

degree of positive or negative reaction to the pill paralleled the degree of "yes" or "no" improvement as noted in Fig. 2. The questionable reactors remained the same in all groups.

Figure 4 summarizes the improvement according to chronicity of somatic symptoms.

Since improvement is approximately the same in three groups (sick over 10 years, one to 9 years, and less than one year), there would seem to be no relationship between improvement and chronicity of the somatic symptom. There were no "questionable" patients in the "less than one year" group. The "questionable number of years" group consists of patients who were vague and indefinite as to length of illness and symptomatology. This particular group ("questionable years") had the highest percentage of therapeutic failures. This is an exceptional group which requires further study.

Chi-square analysis of all four groups reveals significant differences at a probability level, $P<.07$. Further analysis reveals that this difference is almost entirely due to the "questionable years" group. The remaining three groups form a statistically homogeneous population.

Figure 5 summarizes the pill reactors according to chronicity of somatic symptoms.

The majority of patients are pill reactors of the positive or negative type. The "questionable number of years" group has the greatest percentage of questionable reactors to the pill. The percentage of questionable reactors in the "less than one year" group seems to parallel that of the above-mentioned group.

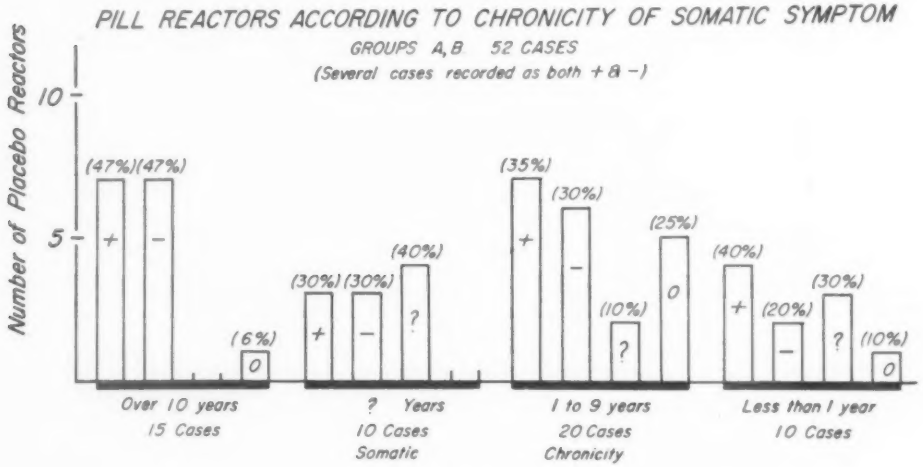


Fig. 5.

OBSERVATIONS ON SPECIAL GROUPS. 1. When the patients were divided into groups according to chronicity of somatic illness (Fig. 4), 9 patients (12%) of the entire series of 75 could not be classified definitely and were put into a special group which we labeled the "questionable number of years" group. A careful study of the patients in this group revealed that they were indeed

unique not only in clinical psychological manifestations, but also unusual in their therapeutic responses.

Clinically, they were at first vague about the length of time they had been ill. They did not volunteer historical data or develop chronological stories of what was wrong with them. Their symptoms were incompletely and inadequately described. Pinning them down was difficult and frustrating. These responses coincide with the "approximate answers" of what we might call "verbal past-pointing" labeled "Vorbeireden" by Ganser in 1898[7,12].

Therapeutically, the "questionable number of years" group had 6 (67%) who failed to improve, while all the other groups recorded more improvements than failures (Fig. 4). Also, this same unique group had a higher percentage of negative and questionable pill reactors than any of the other groups (Fig. 5).

This suggests that this group of patients calls for further study and interpretation.

2. The clinical improvement in 16 patients (21.3%) who were ill 10 years or longer was 56% (Fig. 5). This would indicate that chronicity of somatic symptoms does not preclude successful psychotherapy.

Discussion. The patients invested the pills with a wide range of intellectual and emotional meaning. In some they were seen as modern magic. On the other extreme, they were accepted merely because the physician offered them and without any faith in their efficacy. There seemed to be no limit to the possible somatic and psychic systems which might be influenced for better or for worse. Several patients showed responses which varied from time to time. Naturally, the factors which determined the individual's responses were under constant scrutiny. Further observations on placebo therapy are derived from the clinical data.

Placebo therapy, the most common of all therapies[4,13], by paradox has a scanty literature with but few references. There are no comprehensive lists of indications, contraindications, records of its successes and failures, no reports on its methods of actions or formulations of its dynamics[8]. The subject receives scant notice in textbooks on treatment, and is often ignored in lectures and courses in therapeutics. Meanwhile, physicians have known that placebos can influence the body physiology[2,3,4,10,14,15] and each doctor has one or more faithful and grateful patients who have responded favorably, even dramatically.

Recent medical literature suggests that placebo medication is being subjected to more extensive scrutiny[1-15].

For better understanding it is necessary to distinguish between the "placebo" itself and the "placebo reaction." The "placebo" is the agent employed, with or without some ritual, but always with the suggestion or implication of its power or helpful properties. In the mind of the public, the placebo is a pill made of sugar or some bitter substance. Frequently it is colored. The placebo, however, may be of any object or substance, such as a stone or a vitamin, and may be given by hypodermic or other method. It must never be forgotten that any therapeutic substance (even penicillin and gamma globulin) can in some instances produce a "placebo reaction"[2,3,4,10,14,15]. The placebo part of its action, therefore, cannot be attributed to the intrinsic properties of the substance itself.

The witch doctor with his secret potions and powders, the foods and rituals of the faddist, even the religious symbols and substances which are carried, touched or eaten would all fall into the category of the placebo. The reac-

tion can be produced by serious people, charlatans, scoundrels and scientists with equal facility. Perhaps this fact is one of the many explaining why the progress of the placebo therapy from the magic to the scientific has been so painfully slow.

The "placebo reaction" is the physiological[14,15] and psychological reaction to the administration and acceptance of the placebo. It can also follow a ritual, a surgical procedure and even psychotherapy. This reaction can be positive and beneficial, or it can be negative and detrimental. For completeness sake, we must include the fact that at times the placebo may be offered, but no placebo reaction follows. At other times, the reaction occurs when no placebo intent was considered or intended.

The "placebo reaction" can be peculiar to the individual (even varying in him from time to time) or similar in families, groups or even entire cultures. It appears that the human capabilities for response in this manner are so fundamentally basic and psychologically primitive that the existence of a "placebo reaction" can have no psychiatric diagnostic significance in itself. This means that all humans, even the most maturely adjusted, may, as a result of suffering and longing for relief, obtain a placebo reaction to the medication regardless of its nature. Especially may the response include varying amounts of placebo reaction if the healer is held in great esteem.

Placebo therapy should not be discarded in general practice. It only needs to be put in its place. If, while the patient is being prepared to accept psychotherapy, medication seems necessary, a placebo may be given. We would suggest that always some discussion of present problems, conflicts and worries, go along with it until such time as the pill or injection can be discontinued without threatening the doctor-patient relationship. For the physician who dislikes psychotherapy or feels inadequate to attempt it, we suggest more study of the placebo reaction and more referrals to the psychiatrist. Obviously, specific solutions to tension and stress-producing problems with understanding, insight and maturing is the only therapy which stands the test of time. Nonspecifics will be at best, only temporary.

The awareness of the existence and potency of the placebo is apparently common knowledge. In our study, although the physician himself did not know which pill was placebo, and never mentioned the possibility of placebo therapy, several patients suspected it. Some expressed their interest. Others, in periods of suspicion, curiosity or negativism, made a test. They tried dissolving it in water, assuming it was sugar if it disappeared. Others tasted it or broke it apart to examine it and see if it were bitter or not. Naturally, a placebo given by hypodermic could never be tested in this manner.

The detrimental consequences of the patient discovering that he has been receiving a placebo would dictate that several rules be adopted to protect the doctor-patient relationship. Firstly, the placebo intent must be the confidential secret of the therapists. Secondly, to maintain the integrity of the therapeutic effort, a substance should be used which could influence pharmacologically some somatic symptoms, even though the intent is the placebo reaction. Thus, should a patient become suspicious of placebo therapy, the therapist need only give an honest evasion, rather than a lie. Indeed, the jungle medicine man knew the importance of this long before his scientific colleagues.

The clinical responses to the placebo

parallel the various emotional investments of the doctor-patient relationship. Several patients reported dramatic somatic and psychic changes with the pills after years of failure with various other medications and therapies. The new factor was not so much the pill, but the emotional relationship with the therapist, with the credit displaced to the pill. The patient who called a physician a "magic doctor" had a vague understanding of the real source of her change. There can be no doubt that the placebo derives its power from the vast potential of the emotional relationship between the omnipotent physician and the needs of the patient. The power of the doctor-patient relationship has been noted by others[1]. At times the pill will cement the relationship; at other times it may symbolically or magically distort it. In all instances the placebo is invested as a part of the source, the physician himself.

The statistical results of the therapy have indicated that most patients do not need a placebo to facilitate the doctor-patient relationship. In fact, while in some instances the pill did seem to help, in a greater degree it complicated and made the psychotherapy more difficult. This observation has been noted previously[5]. It would seem logical to hope, however, that future study might indicate those patients in whom a placebo would be beneficial and that the psychodynamic problems presented by the pill's presence would not be a burden detrimental to insight.

There can be no question that the placebo reaction functions within the limits of practical psychotherapy. While the placebo reaction alone may be helpful in some instances, it rarely stands the test of time. The disappearance of the dramatic changes as the pill "loses its charm" is frequently accompanied by grievous emotional reactions. For this reason it is essential to remember that only insight can adequately and permanently solve problems. The pill is not a substitute for expert psychotherapy. On the other hand, if the pill can function in a positive supportive and adjunctive role for a limited time, it will have a place in scientific therapy. In this regard, it is preferable to consider placebo therapy during periods in which the stress is limited by definite time periods, rather than for chronically disturbed persons.

Summary and Conclusions. 1. Seventy-five patients with psychosomatic symptoms were divided into three fairly equal groups. Group A received a potent pill depressing the autonomics and the central nervous system. Group B received a placebo. Group O received no pill medication. All three groups received analytically-oriented psychotherapy. The identity of the potent pill and of the placebo was unknown to the investigators.

2. Therapeutic results were recorded by both patient and physician. The pill group and the placebo group could not be differentiated by numbers of improved patients. The group receiving psychotherapy alone had the highest rate of improvement. Most patients reacted emotionally to both potent pill and placebo.

3. A placebo may be any object offered with therapeutic intent. The placebo may or may not produce a "placebo reaction" which is either subjective or objective, psychological or physiological, and positive or negative. The "placebo reaction" has no psychiatric diagnostic significance.

4. The "potency" of the placebo is derived from, and is a part of, the emotionally-invested doctor-patient relationship. Its therapeutic ranges are

the extremes of practical psychotherapy. Most patients did better in our hands without placebo therapy. The "placebo reaction" occurs in psychotherapy, even without a pill, in the so-called "transference" cure. Specific indications for placebo therapy are not yet available, but placebo therapy should be an adjunct to psychotherapy.

5. It is concluded that placebo therapy should be the secret of the therapists, that a substance conceivably influencing some somatic symptom be used as the placebo, and that placebo therapy be time-limited to periods of increased stress.

6. Important incidental observations included those on a special group of patients characterized by their vagueness; and also the favorable response obtained in a group of patients ill longer than 10 years.

ACKNOWLEDGMENT: We are indebted to Allen C. Miller, M.D. for his assistance with the clinical cases.

REFERENCES

1. **Balint, M.:** Lancet, **1**, 683, 1955.
2. **Beecher, H. K.:** Science, **116**, 157, 1952.
3. **Beecher, H. K., Keats, A. S., Mosteller, F.,** and **Lasagna, L.:** J. Pharm. & Exper. Therap., **109**, 393, 1953.
4. Conference on Therapy: New York State J. Med., **46**, 1718, 1946.
5. **English O. S.:** Med. Rec., **143**, 384, 1936.
6. **Findley, T.:** Med. Clin. N. America, **37**, 1821, 1953.
7. **Ganser, S.:** A.M.A. Arch. Psychiat., **30**, 633, 1898.
8. **Pepper, O. H. P.:** Am. J. Pharm., **117**, 409, 1945.
9. **Ross, O. B., Jr.:** J. Am. Med. Assn., **145**, 72, 1951.
10. **Shapiro, A. P., Myers, T., Reiser, M. F.,** and **Ferris, E. B., Jr.:** Psychosom. Med., **16**, 478, 1954.
11. *Time* Magazine, **64**, 65, 1954.
12. **Weiner, H.,** and **Braiman, A.:** Am. J. Psychiat., **111**, 767, 1955.
13. **Weiss, E.,** and **English, O. S.:** Psychosomatic Medicine. Philadelphia: W. B. Saunders Co., 1949, p. 194.
14. **Wolf, S.:** J. Clin. Invest., **29**, 100, 1950.
15. **Wolf, S.,** and **Pinsky, R. H.:** J. Am. Med. Assn., **155**, 339, 1954.

(Interlingua on page 599)

EFFECTS OF CORTISONE ON METABOLIC RESPONSES IN MYOCARDIAL INFARCTION*

By Gordon G. Bergy, M.D.
TRAINEE, NATIONAL HEART INSTITUTE, 1954–1955

Robert W. Burroughs, M.D.
TRAINEE, NATIONAL HEART INSTITUTE, 1954–1955

AND

Robert A. Bruce, M.D.
ASSOCIATE PROFESSOR OF MEDICINE

(From the Department of Medicine, University of Washington School of Medicine, Seattle, Washington)

Reports concerning the efficacy of steroid hormone therapy in myocardial infarction have been contradictory. Breu[1] has stated that mortality was decreased, blood pressure was stabilized and that electrocardiographic evolution was hastened. Griffith[3] noted no alteration of the course of 12 infarct patients with shock treated with ACTH or cortisone. Sampson and Zipser[4] found hydrocortisone helpful in addition to pressor amine therapy of shock.

Hypotensive and metabolic responses to myocardial infarction in elderly patients treated with routine measures already reported[2] suggested further evaluation of cortisone therapy in the light of these conflicting findings.

Material and Methods. Five patients with typical clinical evidence of myocardial infarction, ranging in age from 52 to 70 years with a mean of 64, were transferred to the Metabolic Ward of King County Hospital (Table 1). No effort was made to select either good or poor risk patients. Pathologic Index Rating (Schnur[5]) ranged from 15 to 135. Three were in heart failure, 2 had experienced angina and previous myocardial infarction. Electrocardiograms demonstrated anterior wall infarction in 4 individuals and posteroseptal infarction in one.

These patients were treated with cortisone, 75 mg. orally every 6 hours; this therapy was started within 48 hours of onset of infarction. Cortisone dosage was tapered 25 mg. daily after the 12th day; this was followed by ACTH, 15 units I.M. daily for 2 days. Supportive therapy included nasal oxygen, morphine, and digitalis for heart failure. Anticoagulants were not used. Neosynephrine and norepinephrine were given to one patient (I.M.), who was in shock.

Pulse, respiration and blood pressure were determined at hourly intervals around the clock for 2 weeks. Four hundred milligram sodium diet was employed; daily intakes of sodium, potassium, and water were calculated from measured amounts of food and fluids. Urinary outputs of sodium and potassium were determined, for calculation of balances. A crude water balance (neglecting insensible and sweat losses) was obtained by subtracting output from intake. Body weight was obtained daily with an Invalift scale. Serum sodium and potassium concentrations, leukocyte count, sedimentation rate (Wintrobe), venous pressure, and circulation time were determined twice weekly. Electrocardiograms were done daily for the first week, then twice weekly through the fifth week.

Hypotension was defined as a systolic pressure under 90 mm. Hg.

Results. 1. CLINICAL COURSE AND MORTALITY RATE (Table 1). Two patients with pathological indices of 80 and 135 expired on the tenth and twelfth days with extensive infarction and heart failure.

Two of the patients who lived experienced hypotension without clinical evidence of shock. Those who died exhibited higher blood pressures dur-

*These studies have been supported by Grant-in-Aid from Washington State Heart Association.

TABLE 1.—CLINICAL SUMMARY

Patient and age		H.N.—66	B.—70	H.J.—70	I.M.—52	B.Z.—64
ECG—Localization of infarct		Anterior	Anterior	Anterior	Postero-septal	Recent anterior, old posterior
History of previous infarct		0	0	0	+	+
Admission B.P.		85/70	178/110	120/80	120/88	130/70
Heart failure	Admission	0	+	0	+++	++
	Hospital course	++	++	0	++++	++
Clinical evidence of shock	Admission	0	0	0	++++	0
	Hospital course	0	0	0	++++	0
Complicating diseases		0	Emphysema Elevated BUN	Obesity	0	Cerebral thrombosis Active duodenal ulcer
Admission—Pathologic Index Rating		35	40	15	135	80
Therapy	Digitalis	+	+	0	+	+
	Vasopressors	0	0	0	Neosynephrine	0
	Anticoagulants	0	0	0	Norepinephrine 0	0
Outcome		Survival	Survival	Survival	Death - day 10, necropsy: infarct anterior and postero - septal walls of left ventricle	Death-day 12 from extension of infarct; no necropsy

ing the course of hospitalization. After the first day, mean hourly systolic pressures varied from 10 to 29 mm. Hg above corresponding levels observed in living patients (Fig. 1). Average diastolic pressures also varied from 11 to 24 mm. Hg higher in dying patients. Heart rate was slightly higher, on the average, in the 2 patients who subsequently died.

2. METABOLIC RESPONSES. All patients had satisfactory caloric intakes after the second day (Fig. 2). During the first week, mean body weight showed negligible fluctuations. One patient, who died, gained 2 kg. before death on the ninth day. The other 4 patients lost 1.0 to 2.1 kg. during the second and third weeks. Discrepancies between weight change and crude water balance

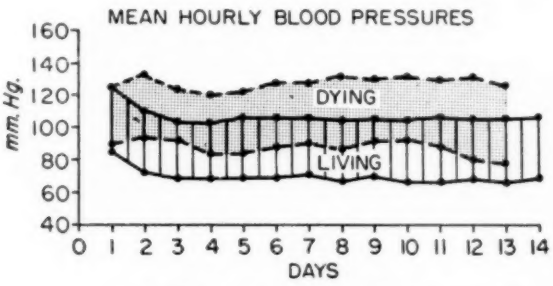


Fig. 1.—Blood pressures were determined at hourly intervals around the clock for 2 weeks. Average daily systolic and diastolic pressures for living patients are compared graphically with corresponding values for dying patients.

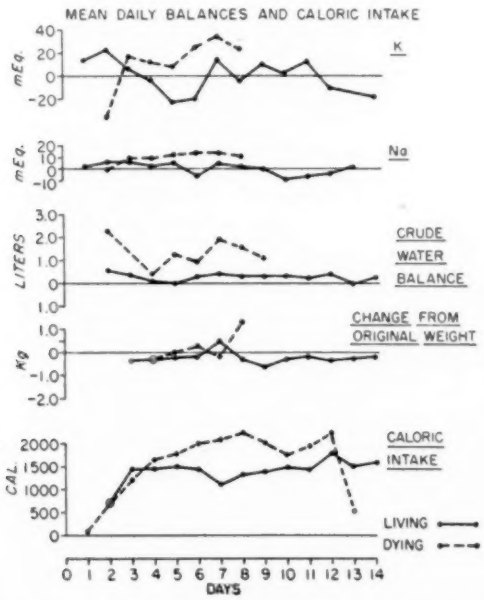


Fig. 2.—Average daily sodium, potassium and crude water for living patients are compared with corresponding data for dying patients. Caloric intake for both groups is indicated.

were observed, and definite water retention was suspected in 2 patients who died, since they retained 0.1 to 2.8 liters per day, or a total of 12.4 and 5.9 liters by the ninth day. This was in contrast to 0.0 to 0.6 liter per day for a mean total of 2.4 liters in survivors on the same day of illness (Fig. 2).

Sodium retention in 2 dying patients never was more than 16 mEq. per day. The total was only 88 and 68 mEq. of sodium on the days of death (Fig. 2). Curiously, potassium balance was also slightly positive (ranging from +5 to 5.4 mEq.) after the second day. This totaled +79 and +125 mEq. at death, even though no potassium supplements had been given (Fig. 2). In these 2 patients, serum sodium fell from 147 to 140 mEq./L. and potassium also decreased from 5.7 to 5.4 during the same time (Fig. 3). There was no potassium loss or significant sodium retention in patients who lived. Serum chloride levels fell from 103 to 97 mEq. in survivors, and from 94 to 91 mEq. in the 2 patients who died.

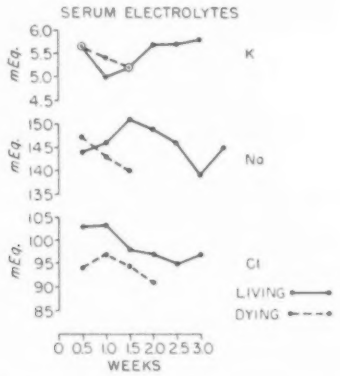


Fig. 3.—Serum potassium, sodium and chloride concentrations were determined at least twice weekly. Biweekly average values for living patients are contrasted with similar values for dying patients.

3. OTHER LABORATORY OBSERVATIONS. Sedimentation rate remained above 22 mm. per hour during the first 2 weeks in all but one patient; all except one exhibited moderate leukocytosis. Venous pressure was elevated in 3 patients on admission and remained elevated in 2 of these, one of whom died. Digitalis was instituted in 3 patients; one died in heart failure, another recovered promptly, and the third recovered after 3 weeks of heart failure. Prolongation of circulation time paralleled venous hypertension in all but one individual.

Electrocardiographic evidences of infarction did not regress or stabilize more rapidly than in untreated individuals. Q waves, RST elevation, and inversion of T waves persisted until death in 2 patients. Q waves accompanied by T inversion were still noted in the fourth week in 2 patients who survived.

Discussion. In this small group, neither morbidity nor mortality was significantly influenced by cortisone therapy. Death occurred in 2 patients as predicted by Pathologic Index Rating on admission. There was neither a "stabilizing effect" on blood pressure, nor prevention of hypotension. Lower blood pressures were observed in 3 survivors; systolic pressures below 90

(and even below 80 in one Oriental patient) were not accompanied by shock. Evolution of electrocardiographic changes was not accelerated. Other evidences of tissue injury or necrosis, such as leukocytosis and elevation of sedimentation rate, persisted as long as usual.

Only the dying patients retained both salt and water and gained weight. This phenomenon, which appears to be primarily a function of the underlying disease[2], may be augmented by cortisone therapy. Survivors are able to maintain normal salt and water metabolism, despite steroid therapy. It was of interest that potassium balance remained slightly positive though no supplements were used.

No other undesirable side effects of cortisone were noted.

Summary. Five patients with acute myocardial infarction were treated with oral cortisone, 300 mg. daily, during the first 12 days of disease. Moderate sodium and water retention occurred in two severely ill patients who died, but did not occur in three patients who lived. Blood pressure responses, morbidity and mortality rate were not favorably influenced.

REFERENCES

1. **Breu, W.:** Munchen. med. Wchnschr., **93**, 666, 1951.
2. **Bruce, R. A., Kowalski, H. J.,** and **Bergy, G. G.:** Circulation, **12**, 207, 1955.
3. **Griffith, G. C., Wallace, W. B., Cochran, B., Nerlich, W. E.,** and **Frasher, W. G.:** Ibid., **9**, 527, 1954.
4. **Sampson, J. J.,** and **Zipser, A.:** Ibid., **9**, 38, 1954.
5. **Schnur, S.:** Ann. Int. Med., **39**, 1023, 1953.

SUMMARIO IN INTERLINGUA

Effectos de Cortisona Super le Responsas Metabolic in Infarcimento Myocardial

Cinque patientes con acute infarcimento myocardial esseva tractate con doses oral de 300 mg de cortisona per die durante le prime 12 dies del morbo. Moderate grados de retention de natrium e aqua occurreva in duo severmente malade patientes qui moriva, sed iste phenomeno non occurreva in le tres altere patientes qui superviveva. Le responsas de pression sanguinee, le morbiditate, e le mortalitate non monstrava un favorabile effecto del droga.

CORRELATION OF PAIN AND THE ROENTGENOGRAPHIC FINDINGS OF SPONDYLOSIS OF THE CERVICAL AND LUMBAR SPINE

By Allen E. Hussar, M.D.

and

Emanuel J. Guller, M.D.

(From the Medical and Radiological Services of the Veterans Administration Hospital, Montrose, New York)

In this report, the term "spondylosis" denotes the roentgenographic findings of bony spurs of the vertebral bodies, narrowed disc space, and narrowed intervertebral foramina, occurring singly or in various combinations. "Spondylosis" is used to differentiate this entity from "degenerative joint disease" (also called osteoarthritis, hypertrophic arthritis, or degenerative arthritis) the name for hypertrophic and degenerative changes in the costovertebral and apophyseal junctions, the only true joints of the spine. Unfortunately, this distinction in pathology and terminology is not respected by the majority of physicians. The aforementioned roentgenographic changes are usually grouped under "degenerative joint disease" or one of its synonyms, causing confusion in the discussion and understanding of these subjects.

Although spondylosis and degenerative joint disease of the spine may be present simultaneously, there is a great difference in their incidence and clinical significance. These differences alone are ample reasons why the two conditions should be handled as two entirely separate entities.

The attitude of the medical profession toward spondylosis as a cause of pain is far from consistent. It has often been written or stated that spondylotic changes rarely, if ever, are responsible for the patient's complaint of neckache or backache. Everyone has had the experience of seeing roentgenographic signs of severe spondylosis in persons without any symptoms. Yet, it is a common practice to consider roentgenographic findings of bony proliferations of the vertebral bodies, narrowed disc space or narrowed intervertebral foramina as the cause of pain over the involved area. Today, it appears to take a certain amount of courage on the part of the physician to disregard those prominent bony spurs seen on the roentgenographic films of the patient who is seeking medical attention for an acute or chronic backache. It may be that well controlled studies to uncover the association of pain with spurs could furnish this much needed courage. With this aim in mind, we undertook the study presented here.

Definite knowledge of the relationship between pain and roentgenographic findings of spondylosis would be important in clinical practice as well as in military, industrial and compensation medicine. To illustrate the significance and magnitude of the problem, we wish to quote this example: From the files of a single geographic area, we have estimated that on a national basis, one of the compensation agencies is currently paying disability pensions to about 30,000 individuals for "osteoarthritis of the spine," with the diagnosis based on backache

and roentgenographic findings of spondylotic changes.

Only a few reports are available on the correlation of pain and spondylotic changes. Although various terminology has been used, all reports quoted here deal with roentgenological findings that come under the term spondylosis.

In Garvin's series[6] of 500 patients with roentgenographic evidence of "hypertrophic arthritis" of the lumbar spine, 30% complained of backache. In another study, 931 industrial job applicants without symptoms referable to the spine and negative findings on rigid physical examination, were submitted to routine pre-employment roentgenographic examination of the lumbosacral spine. "Proliferative changes" were found in 63 cases (Cushway and Maier[5]). In Bohart's experience, "proliferative changes" of the lumbar spine are indications that the individual will work only a short time before becoming disabled by backache[2]. When Breck, Hillsman and Basom[4] examined 450 consecutive applicants for heavy work, none of whom had backache, they found that 21% showed from mild to severe "hypertrophic changes." Recently Biström[1] studied the lumbar spines of 151 patients. While none of them had any painful symptoms, 122 (81%) showed "degenerative changes" of all degrees on the roentgenograms. In Oppenheimer and Turner's observation, thinning of the cervical disc was invariably associated with pain[8]. Others, like Mettier and Capp[7] and Brain[3], could not confirm this close correlation.

The subjects of these few and controversial reports were either persons with pain, patients with various illnesses, or individuals seeking employment. Neither group satisfies the criteria of an objective approach to the problem. Our investigation was undertaken with the thought that sampling the general population might provide better controlled material to re-examine the clinical significance of spondylosis. Only the cervical and lumbar spines, the two most common sites of pain, were included in this study.

Material and Methods. Five hundred male employees of the Veterans Administration Hospital at Montrose, New York, were the subjects of this investigation. For accuracy in this study, we considered it important to obtain a group of individuals who were free of motivation or secondary gain factors, and free of other illnesses or abnormalities. Therefore, the employees were recruited on a voluntary basis after they understood the purely scientific purpose of the examination. Those drawing compensation pensions for "backache," "rheumatism," "arthritis," or those with unsettled claims (a total of only 3 persons) were excluded from this study. Subjects with a history of significant injuries, rheumatoid arthritis, or other systemic diseases were rejected. After physical and roentgenographic examination, those found to have significant abnormalities other than spondylosis were also excluded. The 500 employees investigated came from all ranks and departments in the hospital. They ranged in age from 18 to 65 years, with an average of 36 years.

The investigation consisted of a clinical and roentgenographic examination.

In the course of *clinical* investigation, the individuals were questioned as to the amount of physical work, injuries, and pain in the cervical or lumbar regions and adjacent areas, including radiation into the extremities. A physical examination was carried out to determine excess in weight, limitation of motions, tenderness of the lumbar and cervical areas, also to discover anomalies which would make the subject ineligible for this study.

The *roentgenographic* examination consisted of taking films of the cervical and lumbar spines in anteroposterior, lateral and the two oblique positions. The films were examined for presence of bony spurs, narrowing of disc spaces, narrowing of intervertebral foramina, and abnormalities of the apophyseal joints. Those with other deviations from normal were eliminated from the investigation.

The clinical examination was carried out by one author, the roentgenographic examination by the other. Neither knew the findings of the other until all data were collected.

The results were then submitted to statistical analysis.

Results. I. CERVICAL SPINE. The findings of this investigation were analyzed from the following standpoints.

1. General Correlation of Pain and Roentgenographic Findings. Thirty-eight of the 500 subjects complained of cervical pain and 84 showed roentgenographic signs of spondylotic changes. The numerical correlation of pain and roentgenographic findings is shown in Table 1. When these figures were submitted to statistical evaluation, the following report was returned: "The phi coefficient* transformed to an estimate of Pearson *r* was employed for use with 2 X 2 tables and dichotomized noncontinuous data. Results for cervical roentgenographies yielded a phi of +0.134. This is a correlation which for this number of cases is significantly beyond zero but, on the other hand, is completely worthless for use in prediction of the individual case."

TABLE 1.—ASSOCIATION OF PAIN AND ROENTGENOGRAPHIC FINDINGS OF THE CERVICAL SPINE.

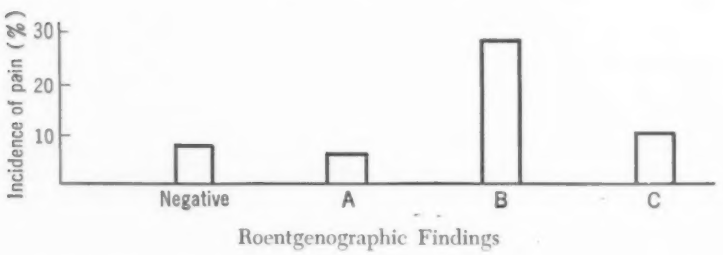
	Pain	*No Pain*
Positive roentgenogram	13	71
Negative roentgenogram	25	391

2. Correlation of Severity of Roentgenographic Findings and Incidence and Severity of Pain. The positive roentgenographic findings were classified into three degrees: A) spurs only, B) spurs and narrowed disc space, C) spurs, narrowed disc space and narrowed foramina. The 5 cases with narrowed disc space but no other findings were put in Group B. The severity of pain was graded as: localized infrequent, frequent, or radicular pain.

The numerical and graphic relationship between these elements is shown in Table 2. Since the incidence of pain was too low for valid statistical analy-

TABLE 2.—CORRELATION OF TYPE OF ROENTGENOGRAPHIC FINDINGS WITH INCIDENCE AND SEVERITY OF PAIN OF THE CERVICAL SPINE (SEE TEXT FOR CLASSIFICATION OF ROENTGEN-RAY FINDINGS. FIGURES IN PARENTHESES MEAN PERCENTAGE.)

			Type of Pain		
Roentgenographic Findings	*Total No.*	*Incidence of Pain*	*Infrequent Localized*	*Frequent Localized*	*Radicular*
Negative	416	25 (6.0)	18 (4.25)	7 (1.65)	0
A	21	1 (5.0)	1 (5.0)	0	0
B	32	9 (28.0)	8 (25.0)	1 (3.0)	0
C	31	3 (10.0)	1 (3.3)	2 (6.6)	0
	500	38	28	10	



*As described in **Edwards, A. L.:** Statistical Analysis for Students in Psychology and Education. New York: Rhinehart & Company, 1951, pp. 117–122.

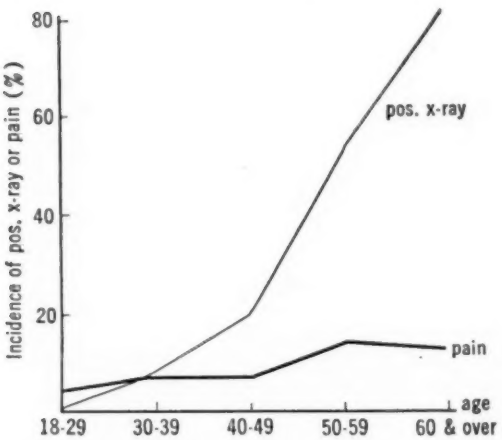
sis, none was performed. However, inspection of the figures fails to reveal any appreciable difference in incidence of pain in the various roentgenographic groups.

The correlation between the severity of roentgenographic findings and severity of pain could not be analyzed because of the small number of cases in the various pain groups. However, note the absence of a single case of radicular pain, even the scarcity of "frequent localized pain" (a total of 3) among the 63 individuals who showed narrowed disc space (roentgenographic Group B plus C). Thirty-one of the 63 also had narrowed intervertebral foramina and in 23 of these 31 persons intraforaminal bone spurs were also seen. Hypertrophic changes of the facet-joints were noted in only 2 cases; neither one had complained of pain.

3. Correlation of Age, Incidence of Positive Roentgenographic Findings and Incidence of Pain. The numerical and graphic relationship between these factors is shown in Table 3. The statistical analysis reveals a highly significant association between the distribution of age and positive roentgenographic findings (chi square = 144.8; $P<0.001$), and only slightly better than chance association between age and incidence of pain (chi square = 10.00; $0.02<P<0.05$).

TABLE 3.—CORRELATION OF AGE, POSITIVE ROENTGENOGRAPHIC FINDINGS AND INCIDENCE OF PAIN OF THE CERVICAL SPINE. (FIGURES IN PARENTHESES MEAN PERCENTAGE.)

Age	*Total No.*	*Positive Roentgen-ray*	*Incidence of Pain*
18–29	147	1 (0.7)	6 (4.0)
30–39	185	15 (8.1)	14 (7.5)
40–49	90	19 (21.1)	7 (7.7)
50–59	55	30 (54.5)	8 (14.5)
60 and over	23	19 (82.6)	3 (13.0)
	500	84	38



4. Correlation of Body Weight, Positive Roentgenographic Findings and Pain. The numerical and graphic re-

lationship between these factors is shown in Table 4. The statistical analysis found a lack of any significant correlation between weight and roentgenographic findings (chi square = 5.8; $0.05<P<0.10$) or weight and pain (chi square = 1.8; $P>0.20$).

5. Correlation of Heavy Work, Positive Roentgenographic Findings and Pain. The numerical and graphic relationship between these factors is shown in Table 5. The statistical evaluation found a better-than-chance association between the degree of heavy work and positive roentgenographic findings (chi square = 10.11; $P<0.01$) but report of pain and degree of work showed in effect only a chance association (chi square = 3.37; $0.10<P<0.20$).

II. LUMBAR SPINE. The findings concerning the lumbar spine were analyzed in the same manner as those of the cervical spine.

1. General Correlation of Pain and Roentgenographic Findings. Of the 500 subjects examined, 95 complained of lumbar backache and 115 showed some radiographic signs of spondylosis. The numerical correlation of pain and roentgenographic findings is shown in Table 6. Statistical analysis of these data found the following correlation: "Results on the lumbar spine yield no relationship between pain and spondylosis."

2. Correlation of Severity of Roentgenographic Findings and Incidence and Severity of Pain. The positive roentgenographic findings are classified into three degrees: A) spurs only, from slight to moderate degree, B) spurs only, of severe degree, C) spurs

TABLE 4.—CORRELATION OF WEIGHT, POSITIVE ROENTGENOGRAPHIC FINDINGS AND INCIDENCE OF PAIN OF THE CERVICAL SPINE. (FIGURES IN PARENTHESES MEAN PERCENTAGE.)

Weight	*Total No.*	*Positive Roentgen-ray*	*Incidence of Pain*
Normal	322	43 (13.3)	24 (7.4)
10–20% over normal	115	24 (20.9)	6 (5.2)
20%–30% over normal	48	14 (29.0)	6 (12.5)
More than 30% over normal	15	3 (20.0)	2 (13.3)
	500	84	38

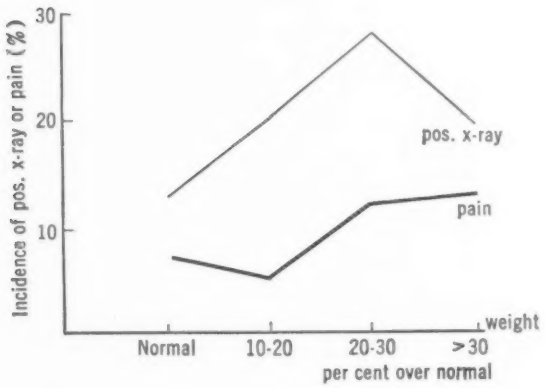
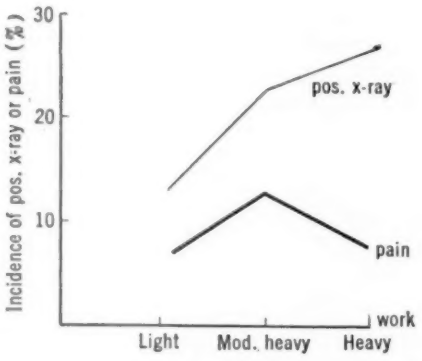


TABLE 5.—CORRELATION OF PHYSICAL WORK, POSITIVE ROENTGENOGRAPHIC FINDINGS AND INCIDENCE OF PAIN OF THE CERVICAL SPINE (FIGURES IN PARENTHESES MEAN PERCENTAGE.)

Physical Work	*Total No.*	*Positive Roentgen-ray*	*Incidence of Pain*
Light	326	41 (12.6)	21 (6.4)
Mod. heavy	79	18 (22.8)	10 (12.7)
Heavy	95	25 (26.3)	7 (7.4)
	500	84	38



and narrowed disc space. The severity of pain was graded as: localized infrequent, frequent, or radicular pain.

No radiologically narrowed intervertebral foramina or intraforaminal spurs were found in this group of subjects.

TABLE 6.—ASSOCIATION OF PAIN AND ROENTGENOGRAPHIC FINDINGS OF THE LUMBAR SPINE.

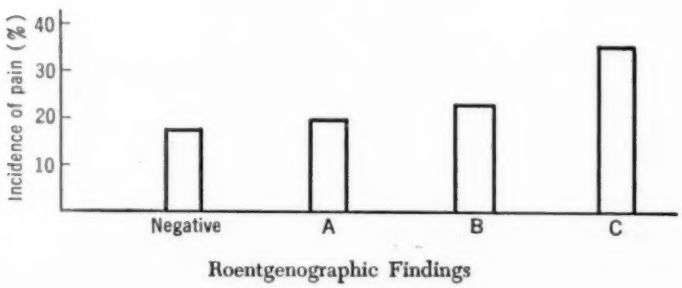
	Pain	*No Pain*
Positive roentgenogram	26	89
Negative roentgenogram	69	316

The numerical and graphic relationship between the three degrees of roentgenographic finding and lumbar pain is shown in Table 7. Statistical evaluation found no correlation between the severity of roentgenographic findings and incidence of pain (chi square and P not significant).

The correlation of severity of roentgenographic findings and severity of

TABLE 7.—CORRELATION OF THE TYPE OF ROENTGENOGRAPHIC FINDINGS WITH INCIDENCE AND SEVERITY OF THE LUMBAR SPINE. (SEE TEXT FOR CLASSIFICATION OF ROENTGENOGRAPHIC FINDINGS. FIGURES IN PARENTHESES MEAN PERCENTAGE.)

			Type of Pain		
Roentgenographic Findings	*Total No.*	*Incidence of Pain*	*Infrequent Localized*	*Frequent, Localized*	*Radicular*
Negative	385	69 (17.9)	36 (9.3)	23 (5.9)	10 (2.7)
A	85	17 (20.0)	12 (14.1)	3 (3.5)	2 (2.4)
B	13	3 (23.0)	1 (7.7)	1 (7.7)	1 (7.7)
C	17	6 (35.3)	3 (17.7)	3 (17.7)	0
	500	95	52	30	13



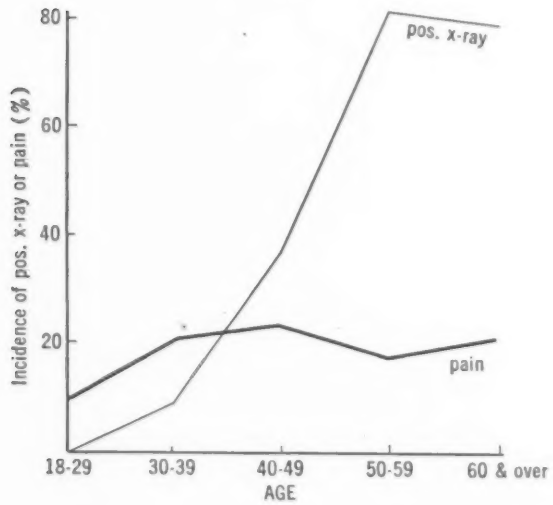
pain was statistically not analyzed because of the very small number of subjects in some pain-groups. Note, however, the absence of radicular pain in the roentgenographic Group C, representing 17 cases with narrowed intervertebral disc space. Of the 13 individuals who complained of radiating pain, 10 had negative roentgenographic findings and only 3 showed spurs of the vertebral bodies. Hypertrophic changes of the facet-joints were only noted in 4 persons, two of them (with A and C degrees of roentgenographic changes, respectively) complained of pain, the other two (also with A and C degrees of roentgenographic changes, respectively) had no pain.

3. Correlation of Age, Positive Roentgenographic Findings and Pain. The numerical and graphic relationship between these factors is shown in Table 8. Statistical evaluation found highly significant correlation between age and positive roentgenographic findings, (chi square = 173.0; $P<0.01$), but no correlation between age and pain (chi square = 5.4).

4. Correlation of Body Weight, Positive Roentgenographic Findings and Pain. The numerical and graphic relationship between these factors is

TABLE 8.—CORRELATION OF AGE, POSITIVE ROENTGENOGRAPHIC FINDINGS AND INCIDENCE OF PAIN OF THE LUMBAR SPINE. (FIGURES IN PARENTHESES MEAN PERCENTAGE.)

Age	*Total No.*	*Positive Roentgen-ray*	*Incidence of Pain*
18–29	147	0	19 (12.9)
30–39	185	18 (9.7)	39 (21.0)
40–49	90	33 (36.7)	22 (24.4)
50–59	55	46 (83.6)	10 (18.0)
60 and over	23	18 (78.5)	5 (21.7)
	500	115	95



shown in Table 9. Statistical evaluation found a better than chance association between weight and positive roentgenographic findings (chi square = 10.5; P= 0.015) but weight and pain showed no significant association (chi square = 1.0; P>0.50).

5. Correlation of Heavy Work, Positive Roentgenographic Findings and Pain. The numerical and graphic relationship between these factors is shown in Table 10. Statistical evaluation of these figures revealed a better-than-chance association between the degree of heavy work and positive roentgenographic findings (chi square = 14.2; P<0.01), but none between hard work and pain (chi square = 3.23; P>0.10).

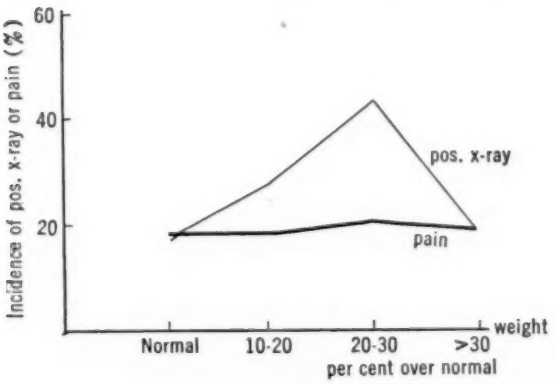
Comments. The task of this clinical investigation was to examine the correlation of the common complaints of neckache and lumbar backache with the common radiographic findings of bony spurs, narrowed disc space and narrowed intervertebral foramina of the cervical and lumbar spines.

Concerning the cervical spine, a low degree of general correlation was found between the incidence of pain and positive roentgenographic findings. This correlation, however, was not high enough to justify the connection of pain with spondylotic changes in individual cases. The value of this correlation was further diminished by the very low degree of relationship between severity of roentgenographic findings and incidence, and severity of pain. Furthermore, a highly significant association was found between age and roentgenographic findings but not between age and incidence of pain.

Concerning the lumbar spine, no

TABLE 9.—CORRELATION OF WEIGHT, POSITIVE ROENTGENOGRAPHIC FINDINGS AND INCIDENCE OF PAIN OF THE LUMBAR SPINE. (FIGURES IN PARENTHESES MEAN PERCENTAGE.)

Weight	*Total No.*	*Positive Roentgen-ray*	*Incidence of Pain*
Normal	322	58 (18.1)	60 (18.6)
10–20% over normal	115	33 (29.0)	22 (19.0)
20–30% over normal	48	21 (44.0)	10 (21.0)
More than 30% over normal	15	3 (20.0)	3 (20.0)
	500	115	95

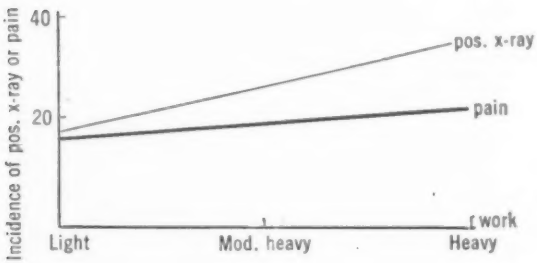


correlation was found between incidence of pain and positive roentgenographic findings. The lack of relationship between these two factors was further substantiated by the facts that while the incidence of positive roentgenographic findings increased with age, body weight and physical work, the incidence of pain did not; furthermore, no correlation could be found between the severity of roentgenographic findings and incidence and severity of pain.

of the 23 persons who showed bony spurs within the cervical intervertebral foramina, none had radicular symptoms and only two complained of pain, localized at the back of the neck. In the case of the lumbar spine, not one of the 17 persons with narrowed disc space had radicular symptoms while of the 13 individuals who complained of pain radiating into the lower extremities, 10 had negative roentgenographic findings and only 3 showed spurs of the vertebral bodies. None of

TABLE 10.—CORRELATION OF PHYSICAL WORK, POSITIVE ROENTGENOGRAPHIC FINDINGS AND INCIDENCE OF PAIN OF THE LUMBAR SPINE. (FIGURES IN PARENTHESES MEAN PERCENTAGE.)

Physical Work	*Total No.*	*Positive Roentgen-ray*	*Incidence of Pain*
Light	326	59 (18.1)	57 (17.5)
Mod. heavy	79	21 (26.5)	16 (20.0)
Heavy	95	35 (37.0)	22 (23.0)
	500	115	95



Pain of radicular distribution is commonly attributed to encroachment upon the radicles of peripheral nerves by bony spurs, degenerated disc or narrowed intervertebral foramina. In our material, not a single individual complained of pain radiating into the shoulders or arms, although 84 had positive roentgenographic findings of the cervical spine, 63 of these showing narrowed disc space and 31 of these 63 also having narrowed intervertebral foramina. It is of greatest interest that these 13 cases showed narrowed disc space or narrowed intervertebral foramina.

Conclusions. The clinical and roentgenographic survey of the cervical and lumbar spine of 500 male hospital employees permits the following conclusions:

1. As a rule, pain is not associated with the roentgenographic findings of bone spurs, narrowed disc space or intervertebral foramina of the cervical and lumbar spine.

2. It is conceivable that pain may be produced by the encroachment of a bone spur, protrusion of a disc or narrowing of a foramen, upon a by-passing nerve trunk, thus producing the symptoms of radicular compression. This occurrence, however, is probably more an exception rather than a natural sequel of spondylosis. Routine roentgenograms are of dubious value in the diagnosis of encroachment on the nerves by spondylotic changes.

3. It is suggested that the common practice of labeling a patient with the diagnosis of "degenerative joint disease" (or "osteoarthritis," "hypertrophic arthritis") of the spine because of roentgenographic findings of spondylotic changes should be abandoned.

ACKNOWLEDGMENT: The authors are indebted to Jerome L. Singer, Ph.D., Chief of Research Section, Clinical Psychology Service, Veterans Administration Hospital, Montrose, New York, for his statistical analysis of the collected data.

REFERENCES

1. **Biström, O.:** Ann. Chir. et Gynaec. Fenniae, **43**, 29, 1954.
2. **Bohart, W. H.:** J. Am. Med. Assn., **92**, 698, 1928.
3. **Brain, R.:** Ann. Int. Med., **41**, 439, 1954.
4. **Breck, L. W., Hillsman, J. W.,** and **Basom, W. C.:** Ann. Surg., **120**, 88, 1944.
5. **Cushway, B. C.,** and **Maier, R. J.:** J. Am. Med. Assn., **92**, 701, 1929.
6. **Garvin, J. D.:** A.M.A. Arch. Surg., **15**, 118, 1927.
7. **Mettier, S. R.,** and **Capp, C. S.:** Ann. Int. Med., **14**, 1315, 1941.
8. **Oppenheimer, A.,** and **Turner, E. L.:** Am. J. Roentgenol., **37**, 484, 1937.

CONCLUSIONES IN INTERLINGUA

Correlation de Pena e de Constatationes Roentgenographic de Spondylosis del Spina Cervical e Lumbar

Le studio clinic e roentgenographic del spina cervical e lumbar de 500 mascule empleatos de hospital permitte le sequente conclusiones:

1. In regula general, pena non es associate con le constatationes roentgenographic de sporones ossee, restringite spatio de disco, o restringite foramines intervertebral del spina cervical o lumbar.

2. Il es concipibile que pena pote esser producite per le impingimento de un sporon ossee, le protrusion de un disco o le reduction del dimensiones de un foramine, super un passante trunco nerval, assi producente le symptomas de compression radicular. Iste occurrentia, totevia, probabilemente es le exception plus tosto que un sequela natural de spondylosis. Roentgenogrammas routinari es de dubitose valor in le diagnose de impingimento super le nervos causate per cambiamentos spondylotic.

3. Nos suggere que on debe abandonar le practica commun de applicar un diagnose de "morbo degenerative del articulos," (o de "osteoarthritis" a "arthritis hypertrophic") a causa de constatationes roentgenographic de cambiamentos spondylotic.

THE ANGIOCARDIOGRAPHIC PATTERN OF HIGH VENTRICULAR SEPTAL DEFECT WITH LEFT TO RIGHT SHUNT

By Louis A. Soloff, M.D.
CLINICAL PROFESSOR OF MEDICINE, TEMPLE UNIVERSITY SCHOOL OF MEDICINE AND HOSPITAL; CHIEF OF MEDICINE, EPISCOPAL HOSPITAL

AND

Jacob Zatuchni, M.D.
ASSOCIATE IN MEDICINE, TEMPLE UNIVERSITY SCHOOL OF MEDICINE AND HOSPITAL; AND EPISCOPAL HOSPITAL

(From the Departments of Medicine, Temple University School of Medicine and Hospital, and Episcopal Hospital, Philadelphia, Pennsylvania)

Defects in the interventricular septum are almost always localized to the base of the heart in the region of the undefended space (Abbott[1]). Such uncomplicated defects permit a left to right ventricular shunt. Although the diagnosis of such a lesion can frequently be made with a fair degree of accuracy on clinical grounds alone, important differences in surgical approaches for other lesions which may mimic it have made objective verification of the diagnosis mandatory (Wood, Magidson and Wilson[5]). Such verification is usually but not always supplied by the technique of cardiac catheterization (Bowers, Burchell and Wood[2]). The use of angiocardiography for this lesion has been ignored because of the prevailing belief that this technique is incapable of demonstrating a left to right ventricular shunt. More recently, Lind, Spencer and Wegelius[3] have described an angiocardiographic pattern which they regard as characteristic for ventricular septal defect with left to right shunt. Their pattern, however, fails to demonstrate the indispensable angiocardiographic finding of such a lesion, reopacification of the right ventricle.

The purpose of this report is to describe, by a detailed analysis of a case, the pathognomonic pattern of a high ventricular septal defect with left to right shunt.

Case Report. L.M., a 17-year-old girl, was admitted to Temple University Hospital on December 6, 1955, to determine the nature of an abnormal cardiac silhouette in a roentgenogram taken during a routine chest survey.

She knew that she was born with a cardiac murmur but never had cardiac symptoms either at rest or upon effort. Her twin sister was a head taller and thirty pounds heavier than she.

Physical examination revealed a slightly built short girl. She weighed 98.5 pounds and was 4 feet 11 inches tall. There were no signs of heart failure. The examination, other than the chest, was not remarkable.

The blood pressure was 110/80 mm. Hg. The chest wall was asymmetric with marked bulging of the anterior wall of the left hemithorax. A systolic shock was palpable in the pulmonic region. P2 was markedly accentuated and louder than A2. The point of maximal impulse (other than the pulmonic one) was palpable in the sixth intercostal interspace at the anterior axillary line. An extremely loud and harsh systolic murmur was heard maximally in the fourth left intercostal interspace parasternally. Here a distinct systolic thrill was palpable. The two heart sounds could be clearly distinguished from the murmur. The murmur faded in all directions over the precordium but was still clearly audible over the posterior inferior wall of the thorax.

The electrocardiogram showed a sinus rhythm with a slightly prolonged P–R interval. The ventricular complexes revealed high R waves in the left precordial leads and

right bundle branch block, a combination compatible with the diagnosis of biventricular hypertrophy.

Fluoroscopic study of the chest revealed prominent and pulsatile pulmonary vascular markings and a moderate increase in the size of the cardiac silhouette with predominant enlargement of the outflow tract of the right ventricle and pulmonary artery.

The presumptive diagnosis was congenital heart disease with ventricular septal defect producing a left to right ventricular shunt. Because other congenital lesions, curable by surgery, could not with certainty be excluded on clinical grounds, our usual laboratory procedures were carried out.

Cardiac catheterization (done by Dr. George E. Mark, Jr.) revealed the following findings:

	Pressure mm. Hg	*Oxygen Vol. %*
Superior vena cava		11.9, 11.9
Right atrium	5	12.0, 12.8
Right ventricle	69/8	15.1, 15.6
Main pulmonary artery	70/48	15.5
Pulmonary artery wedge	15	18.2

Blood from the femoral artery had an oxygen content of 17.6 volumes % and an oxygen capacity of 18.0 volumes %.

Angiocardiography was done immediately after cardiac catheterization.

The degree and duration of opacification of the cardiac chambers and great vessels are shown diagrammatically in Fig. 1. The superior vena cava and right atrial times were each 3.5 seconds. The inflow tract of the right ventricle was best visualized in the anterior projection. The most intense opacification occurred early but was never maximal and disappeared within 3.5 seconds. The outflow tract of the right ventricle likewise opacified early and was slightly more intense than that of the inflow tract but also almost completely disappeared in 3.5 seconds. However, succeeding films showed abrupt maximal opacification of the outflow tract. The degree of opacification slowly decreased but minimal opacification remained to the end of the study. The right ventricular outflow tract time was at least 18.2 seconds. The pulmonary artery, like the outflow tract of the right ventricle, showed early maximal opacification followed by fading and then

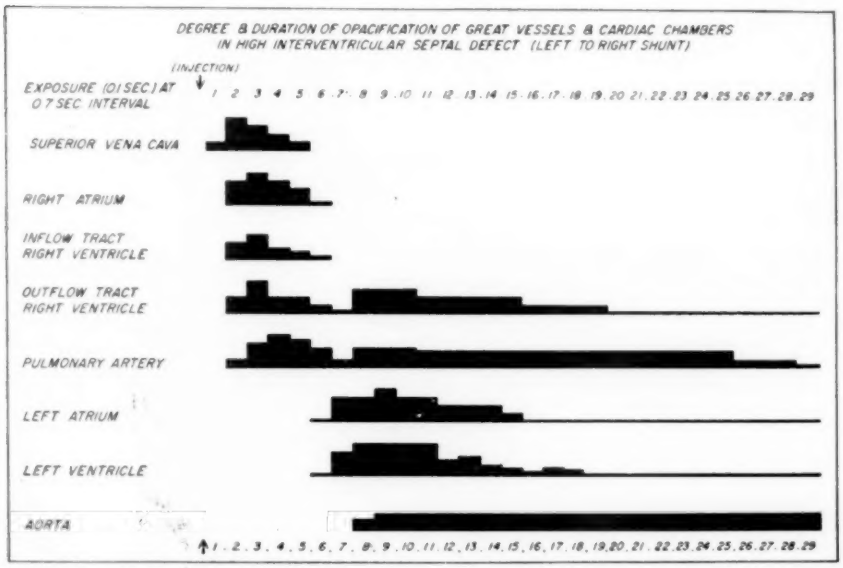

DEGREE & DURATION OF OPACIFICATION OF GREAT VESSELS & CARDIAC CHAMBERS
IN HIGH INTERVENTRICULAR SEPTAL DEFECT (LEFT TO RIGHT SHUNT)
(INJECTION)
EXPOSURE (0.1 SEC.) AT
0.7 SEC. INTERVAL
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29
SUPERIOR VENA CAVA
RIGHT ATRIUM
INFLOW TRACT
RIGHT VENTRICLE
OUTFLOW TRACT
RIGHT VENTRICLE
PULMONARY ARTERY
LEFT ATRIUM
LEFT VENTRICLE
AORTA
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29

Fig. 1.—Diagram of degree and duration of opacification of cardiac chambers and great vessels. Degree of opacification is graded to a maximum of 4. See text for analysis.

abrupt maximal re-opacification. Opacification of the pulmonary artery was also still visible at the end of the study. The pulmonary artery and its branches were markedly enlarged.

The left atrium was slightly enlarged. The angiocardiographic size of the left atrium could not be determined with certainty because the left and inferior borders of the left atrium were not sharply defined. The left atrium and left ventricle were almost equally opacified. Immediately after intense opacification of the left ventricle, contiguous intense opacification of the outflow tract of the right ventricle was seen. The contrast substance extended from the anterior superior

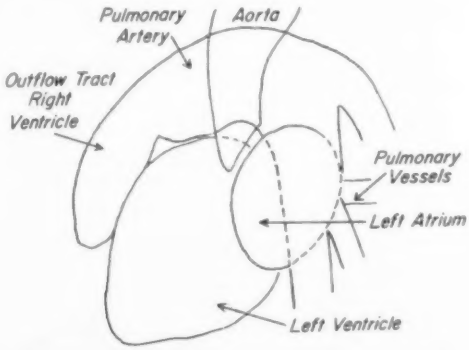


Fig. 2.—Angiocardiogram in the left lateral projection and corresponding illustrative diagram, 4.9 seconds after initial opacification of the right atrium. The inflow tract of the right ventricle is not opacified, nor was it in the anterior projection. There is reopacification of the outflow tract of the right ventricle and pulmonary artery at the time of intense opacification of the left ventricle. Opacification of the left ventricle and adjacent outflow tract of the right ventricle is homogeneous. The shunt is large and passes through the anterior and superior portion of the interventricular septum, slightly below the site of origin of the aorta.

portion of the left ventricle just below the site of origin of the aorta into the outflow tract of the right ventricle (Fig. 2). Opacification of these portions of the heart, together with that of the pulmonary artery and left atrium persisted with diminishing intensities to the end of the study. The aorta also remained opacified to the end of the study.

The left ventricular wall was 10 mm. thick. The left ventricular chamber was slightly enlarged. The intracardiac circulation time was 4.2 seconds, shorter than our average normal (6.3 seconds).

The patient was discharged from the hospital on December 15, 1955.

Discussion. Reopacification of the right ventricle, the indispensable angiocardiographic findings of a left to right ventricular shunt, can be demonstrated with certainty only if the right ventricle shows little or no opacification when opacified blood from the left ventricle first begins to pass through the defect. This demonstration is facilitated by exposing roentgenograms at right angles to the shunt.

Although the greater portion of the ventricular septum is tangential to the frontal plane, its cranial portion, the site of almost all ventricular septal defects, is virtually parallel to it. The lateral projection is, therefore, the one of choice. This projection also permits maximal separation of the significant outflow tract of the right ventricle from the left. In our experience, this projection is also best in minimizing overlapping by the opacified chambers of the left heart, great vessels and even by the spine. However, an additional projection is necessary to recognize change in opacity due to depth alone.

Reopacification of the right ventricle by opacified left ventricular blood alone can be diagnosed only if the right atrium is nonopacified and the right ventricle has been emptied of all or the greater portion of the contrast substance before maximal opacification of the left ventricle occurs. In the infant, such a sequence of events may be difficult or impossible to achieve because of the extremely rapid intracardiac circulation time in contrast to the relatively slow injection of contrast substance. Moreover, reflux of contrast substance from the vena cavae in the infant may further prolong opacification of the right heart. It is, perhaps, for these technical reasons that Lind, Spencer and Wegelius failed to demonstrate an angiocardiographic pattern acceptable to us as pathognomonic of left to right ventricular shunt. We do not know whether the poor opacification of the right ventricle reported by these investigators is actually due to dilution of the opacified right ventricular blood by the nonopacified left ventricular blood or due to the slow return of contrast substance from the vena cavae. In either event, such a pattern is not likely to occur in the older child or adult, in the absence of hepatic reflux or stagnation, because the amount of contrast substance injected (50 ml.) is much more than that needed to produce maximal opacification of the right ventricle and because the intracardiac flow is slower. Indeed, in the absence of reopacification of the right ventricle, this lesion cannot produce a specific picture. This is so because the degree and duration of opacification of various portions of the heart depend not solely on technical factors which can be standardized but also on intracardiac flow which is related in part to chamber size and function (Soloff *et al.*[4]). It is for this reason that the pattern similar to that described by Lind, Spencer and Wegelius cannot be distinguished at least in older individuals from other congenital defects or even from certain types of acquired heart disease which may show prolonged opacification of the right ventricle.

Summary. An instance of high ventricular septal defect with left to right

shunt is described to illustrate the pathognomonic angiocardiographic pattern of this defect. This pattern consists of a rapid intracardiac circulation time and a rapid right heart time followed by reopacification of the outflow tract of the right ventricle contiguous with an immediately preceding opacified left ventricle. The opacification of the left ventricle, outflow tract of the right ventricle, pulmonary artery and aorta are all prolonged. The pulmonary artery and its branches are disproportionately enlarged. The left and right ventricle as well as the left atrium may be enlarged.

REFERENCES

1. **Abbott, M. E.:** Atlas of Congenital Cardiac Disease. New York: American Heart Association, 1936.
2. **Bowers, D., Burchell, H. B.,** and **Wood, E. H.:** Proc. Staff Meet., Mayo Clin., **30**, 261, 1955.
3. **Lind, J., Spencer, R.,** and **Wegelius, C.:** Circulation, **11**, 609, 1955.
4. **Soloff, L. A., Zatuchni, J., Stauffer, H. M.,** and **Kelly, E. W.:** Circulation, **13**, 334, 1956.
5. **Wood, P., Magidson, O.,** and **Wilson, P. A. O.:** Brit. Heart J., **16**, 387, 1954.

SUMMARIO IN INTERLINGUA

Le Configuration Angiocardiographic de Defectos del Septo Ventricular Alte, con Derivation Sinistro-Dextere

Es describite un exemplo de defecto del septo ventricular alte con derivation sinistro-dextere pro illustrar le pathognomonic configuration angicardiographic de iste defecto. Le configuration consiste de un rapide tempore de circulation intracardiac e un rapide tempore dexterocardiac sequite per re-opacification del via de effluxo del ventriculo dextere contigue con un immediatemente precedente opacification del ventriculo sinistre. Le opacification del ventriculo sinistre, del via de effluxo del ventriculo dextere, del arteria pulmonar, e del aorta es omnes prolongate. Le arteria pulmonar e su brancas es disproportionatemente allargate. Le ventriculos sinistre e dextere e etiam le atrio sinistre pote esser allargate.

EXPERIMENTAL MYOCARDIAL INFARCTION: CIRCULATORY, BIOCHEMICAL AND PATHOLOGIC CHANGES*

By Richard J. Bing, M.D.
PROFESSOR OF MEDICINE, CHIEF, WASHINGTON UNIVERSITY SERVICE, VETERANS ADMINISTRATION HOSPITAL, ST. LOUIS, MISSOURI
(FORMERLY PROFESSOR OF EXPERIMENTAL MEDICINE, MEDICAL COLLEGE OF ALABAMA, BIRMINGHAM, ALABAMA)

Alberto Castellanos, M.D.
ASSISTANT IN MEDICINE, MEDICAL COLLEGE OF ALABAMA, BIRMINGHAM, ALABAMA

Erich Gradel, M.D.
FELLOW IN EXPERIMENTAL MEDICINE, MEDICAL COLLEGE OF ALABAMA, BIRMINGHAM, ALABAMA

Charles Lupton, M.D.
ASSOCIATE PROFESSOR OF PATHOLOGY, MEDICAL COLLEGE OF ALABAMA, BIRMINGHAM, ALABAMA

AND

Abraham Siegel, M.S.
FELLOW IN PHYSIOLOGY, MEDICAL COLLEGE OF ALABAMA, BIRMINGHAM, ALABAMA

(From the Departments of Experimental Medicine, Physiology, and Pathology, The Medical College of Alabama, Birmingham, Alabama)

Recent studies on circulatory changes in acute myocardial infarction in man confirm that the primary circulatory alterations are a decrease in cardiac output with a compensatory increase in peripheral vascular resistance[12,25]. The pattern is not uniform, however, as some patients show no increase in peripheral resistance and no fall in stroke volume[12,25]. Wiggers, Kupfer and Orias introduced the concept that compensation of the myocardium following coronary artery occlusion is due to enhanced action of the uninvolved portion of the myocardium rather than an improvement of the circulation through the injured area[17,22,29]. Failure in the ability of the uninvolved myocardium to respond to this burden results in circulatory failure.

Studies from this laboratory have shown that immediately following embolization of the coronary arteries with plastic microspheres suspended in gum acacia solution, there resulted a significant reduction in coronary flow and in the utilization of glucose, pyruvate and lactate[24]. Work in this laboratory has also demonstrated that in dogs and man several hours after coronary occlusion, plasma levels of glutamic oxalacetic transaminase, malic dehydrogenase, phosphoglucose isomerase and

*Original work supported by the U.S. Public Health Service Grant H-1129(C4), the Life Insurance Medical Research Fund, and the American Heart Association.
This paper was read in part at the meeting of the Association of American Physicians at Atlantic City, May 1, 1956.

fructose aldolase were elevated in peripheral blood[3].

Karsner has described the pathological changes in the myocardium following coronary arterial ligation in the dog[16]. These were characterized by local congestion, hemorrhage, edema and cloudy swelling with muscle necrosis. Following this, necrotic tissue was removed by leukocytes, and still later fibroblasts and giant cells were observed. While these events occurred rather rapidly in the dog, a study of myocardial infarction in man by Mallory, White and Salcedo-Salgar indicates a much slower process but the sequence of events appeared to be the same[19].

The purpose of this paper is to describe the circulatory, pathologic and biochemical alterations which follow experimental myocardial infarction in the dog. A correlation will be made of these data in order to aid in comprehending their causal relationship.

Methods. Experimental myocardial embolization was produced in dogs using the method of Agress, whereby plastic microspheres suspended in a 15% solution of gum acacia in normal saline were injected into the coronary circulation (2 mg. of spheres per kg. weight were injected)[1]. The animals were anesthetized with sodium pentathol (30 mg./kg.). Results obtained were compared with those where the suspending medium was the animal's own plasma or human albumin. These media were employed because it was found that the injection of gum acacia solution alone produced some of the hemodynamic and metabolic alterations of coronary occlusion.

Blood gases were determined by the method of Van Slyke and oxygen and CO_2 in expired air by the method of Scholander[23,28]. Blood pressures were photographically recorded with a strain gauge transducer.

Blood glucose was estimated by the method of Hagedorn and Jensen[14] using a Somogyi[26] filtrate, pyruvate by the method of Friedemann and Haugen[11], lactate by the method of Barker and Summerson[2] and ketone bodies expressed as acetone by a modification of the method of Greenberg and Lester[13] by Engel[9]. Plasma transaminase was estimated by the method of Karmen, Wroblewski, and LaDue[15]. Phosphoglucose isomerase, which catalyzes the reaction

$$\text{glucose-6-phosphate} \rightleftarrows \text{fructose-6-phosphate}$$

was determined by the method of Bodansky[7]. Aldolase, catalyzing the reaction

$$\text{fructose,1,6,diphosphate} \rightleftarrows \text{phosphoglyceraldehyde} + \text{dihydroxyacetone phosphate}$$

was estimated by the method of Bruns[8]. Aldolase activity is expressed as micrograms of inorganic phosphate split from the dihydroxyacetonephosphate per ml. of plasma per hour at 38° C.

Malic dehydrogenase was determined by the method previously described[3]. This enzyme catalyzes the reaction

$$\text{oxalacetic acid} \rightleftarrows \text{malic acid.}$$

Cardiac output was determined by the Fick principle[10]. Coronary flow was measured by the nitrous oxide method (Bing *et al.*[6]). Coronary vascular resistance was expressed in mm.Hg/100 gm./min. It is calculated from:

$$\frac{\text{mean blood pressure (mm.Hg)}}{\text{coronary flow (ml./100 gm. left ventricle/min.)}}$$

Peripheral vascular resistance is defined in mm.Hg/L. as:

$$\frac{\text{mean blood pressure (mm.Hg)}}{\text{cardiac output L./min.}}$$

Left ventricular weight was calculated as previously described (Spencer *et al.*[27]).

To evaluate pathologic changes in the myocardium, a total of 23 dogs were studied at varying time intervals (20 minutes to 6 weeks) after embolization of the coronary arteries by plastic spheres. There were 5 animals in the control and 18 in the experimental group. The latter included 7 hearts examined 24 hours after coronary artery embolization and one examined after each of the following time intervals: 20 minutes, 30 minutes, 2 hours, 3 hours, 5 hours, 2 days, 3 days, 4 days, 6 days, 10 days and 6 weeks. Immediately following gross examination, the hearts of control and experimental animals were fixed in neutral formalin. Multiple sections of muscle were prepared and stained with Mallory's hematoxylin and eosin (H&E). Where this procedure revealed microscopic changes, serial sections were prepared and

stained by Mowry's method for Alcian-blue (AB) and McManus' technique for periodic acid-Schiff (PAS), Orcein-vanGieson (O-VG) and phosphotungstic acid hematoxylin (PTAH)[20,21]. The PAS stain identifies carbohydrates. Sections of representative areas were stained for fat with Sudan IV and PAS. Alcian-blue stains acid mucopolysaccharides. Orcein-vanGieson and phosphotungstic acid hematoxylin are elastic tissue stains.

In the statistical treatment of the data, paired algebraic differences were recorded for each animal. Student's test was applied and p values were determined as described by Lacey[18]. A probability value of less than 0.05 was considered significant.

Results. I. CIRCULATORY STUDIES. a) Circulatory effects and myocardial oxygen utilization using gum acacia as the suspending vehicle:

Table 1 summarizes the hemodynamic effects in this series of experiments. Control values are compared for significance with results obtained immediately after embolization. In a series of 9 animals the mean blood pressure showed a significant decrease of 63.4 mm.Hg ($p<0.01$, Table 1). A significant decrease in coronary flow of 92 ml./100 gm./min. was observed in a series of 11 experiments ($p<0.01$, Table 1). In 9 experiments, coronary vascular resistance was not significantly altered ($p>0.3$, Table 1).

Table 1 also summarizes effects obtained in 5 experiments on cardiac output and peripheral vascular resistance. There was a mean decrease in cardiac output of 1.34 L./min., which was not significant ($p>0.05$). On the other hand, the peripheral vascular resistance showed a significant decrease of 19.4 mm.Hg/L./min. ($p<0.01$). Apparently the injection of spheres suspended in gum acacia had resulted in peripheral vasodilatation leading to a drop in mean blood pressure (Table 1). There was, however, no significant change in coronary vascular resistance, since there was a proportionate reduction in both mean blood pressure and coronary blood flow (Table 1).

Immediately after embolization the mean myocardial oxygen extraction rose 2.3 volumes per cent but this change was not significant ($p>0.11$, Table 1). However, as a result of the reduction in coronary flow, the myocardial oxygen usage decreased significantly (9.1 ml./100 gm./min., $p<0.02$, Table 1). Thirty minutes after embolization coronary flow, coronary vascular resistance, peripheral vascular resistance and myocardial oxygen usage had returned to control levels (Table 1). The changes described above are, therefore, rapidly reversible. In a limited number of experiments the injection of a 15% gum acacia solution without spheres resulted in changes in hemodynamics which were qualitatively similar to those described above. As presented in a subsequent paragraph, the injection of gum acacia alone also resulted in changes in myocardial metabolism, similar to those seen after coronary artery embolization with spheres.

b) Circulatory effects and myocardial oxygen utilization using microspheres suspended in dog plasma or human albumin:

In 13 animals of this series, the mean blood pressure showed a significant decrease of 51.3 mm.Hg ($p<0.01$). Coronary blood flow and coronary vascular resistance also fell significantly (21.9 ml./100 gm./min., $p<0.01$) and 0.36 mm.Hg/ml./min., $p<0.01$) (Table 2 and Fig. 1). This was in contrast to the results obtained with gum acacia as the suspending vehicle, where the coronary vascular resistance was not significantly altered.

The cardiac output decreased significantly (1.22 L./min., $p<0.05$, Table 2). In dogs injected with microspheres suspended in plasma or human albumin, the peripheral resistance was not significantly increased (4.43 mm.Hg/L./min., $p>0.05$, Table 2). On the other hand, the animals injected with

TABLE 1.—CIRCULATORY DATA OBTAINED WITH SPHERES IN GUM ACACIA

Date	Weight kg.	Time	Mean B. P. mm.Hg	Oxygen Content: Arterial Vol. %	Oxygen Content: Coronary Sinus Vol. %	Coronary Flow ml/100 gm./min.	Coronary Vas. Res. mm.Hg/ml./100 gm./min.
3-14-56	12	Control	100	17.1	4.9	116	.86
		4 min.	50	20.6	4.5	19	2.3
3-15-56	16	Control	120	14.3	3.9	146	.83
		4 min.	40	16.8	5.5	48	.84
3-19-56	13	Control	100	14.7	4.3	174	.57
		4 min.	50	13.0	—	68	.74
		24 hrs.	60	13.0	4.3	99	.61
		72 hrs.	80	10.6	2.4	157	.51
3-21-56	16.7	Control	120	14.2	4.7	221	.54
		4 min.	10	19.1	2.8	54	.18
3-26-56	10.2	Control	130	14.2	4.0	82	1.57
		4 min.	60	10.0	1.7	44	1.37
3-27-56	20	Control	120	14.1	3.7	216	.55
		4 min.	60	14.8	1.0	37	1.62
		24 hrs.	90	15.3	4.3	210	.43
4-3-56	16	Control	105	13.4	3.1	128	.82
		4 min.	26	12.7	.9	35	.75
		24 hrs.	67	11.5	3.0	165	.91
4-5-56	12	Control	130	16.3	4.6	200	.65
		4 min.	74	—	—	124	.59
		30 min.	136	15.3	4.0	104	1.30
4-6-56	14	Control	73	16.0	2.5	67	1.09
		4 min.	53	—	—	52	1.02
		30 min.	75	16.9	6.4	56	1.34
4-10-56	14	Control	109	16.0	—	87	1.25
		4 min.	—	—	—	39	—
		30 min.	87	16.8	—	73	1.19
4-11-56	12.9	Control	89	13.2	3.3	145	61
		4 min.	—	—	—	52	—
		30 min.	91	12.5	5.4	92	.99
Mean of Diff.			−63.9			−91.8	+0.2145
Range of Observations			−110 to −20			−179 to −15	−0.36 to +1.44
Deg. of Free.			8			10	8
t			7.38			6.38	1.045
p			<0.01			<0.01	>0.8
Conclusions			S			S	NS

TABLE 2.—CIRCULATORY DATA OBTAINED WITH SPHERES IN ALBUMIN AND DOG PLASMA

Date	Weight kg.	Time	Mean B. P. mm.Hg	Oxygen Content: Arterial Vol. %	Oxygen Content: Coronary Sinus Vol. %	Coronary Flow ml/100 gm./min.	Coronary Vas. Res. mm.Hg/ml./100 gm./min.
2-20-56*	18.8	Control	110	12.9	2.1	120	.92
		4 min.	60	13.6	3.6	62	.97
		24 hrs.	90	12.8	3.6	122	.74
3-2-56*	14	Control	110	14.7	2.7	129	.85
		4 min.	75	14.9	5.2	129	.58
3-5-56*	19	Control	120	16.0	3.9	132	.91
		4 min.	75	17.0	5.1	117	.44
3-7-56*	17.7	Control	100	11.6	2.4	76	1.32
		4 min.	60	17.9	5.5	75	.80
3-8-56*	16	Control	125	20.5	5.3	88	1.40
		4 min.	80	20.6	3.8	75	1.07
3-9-56*	14.5	Control	120	14.8	3.6	161	.75
		4 min.	55	16.1	5.2	75	.73
		24 hrs.	100	15.7	4.6	128	.78
4-23-56*	14.5	Control	110	16.2	5.1	85	1.29
		4 min.	50	17.2	8.5	80	.63
4-24-56△	14.7	Control	140	10.6	4.2	151	.93
		4 min.	95	12.2	2.7	155	.61
4-25-56△	17.7	Control	120	18.3	8.4	93	1.29
		4 min.	55	22.0	3.6	52	1.05
4-26-56△	15	Control	110	15.1	4.5	118	.93
		4 min.	50	15.3	5.0	96	.52
4-30-56*	14.9	Control	120	16.0	3.4	80	1.50
		4 min.	55	17.1	4.6	75	.73
5-2-56△	12.4	Control	90	14.5	2.1	123	.73
		4 min.	50	15.0	5.1	71	.70
5-3-56△	17	Control	140	13.9	2.5	91	1.54
		4 min.	90	17.9	2.9	100	.90
Mean of Diff.			−51.3	−1.67	+0.772	−21.9	−0.357
Range of Observations			−65 to −35	+0.1 to +6.3	−4.8 to +3.4	−86 to +9	−.77 to +.05
Deg. of Free.			12	12	12	12	12
t			17.42	3.24	1.205	−2.643	−5.00
p			<0.01	<0.01	>0.2	<0.05	<0.01
Conclusions			S	S	NS	S	S

* Spheres suspended in albumin △ Spheres suspended in dog plasma

TABLE 1.—(*Continued*)

Myocard. O_2 Ext. Vol. %	*Myocard. O_2 Cons. 100 gm./ml./min.*	*Syst. A-V Vol. %*	*Total O_2 Cons. ml./min.*	*Cardiac Output L./min.*	*Cardiac Index*	*Stroke Volume*	*Per. Res. mm.Hg/L./min.*
12.2	14.1	2.7	—	—	—	—	—
16.1	3.1	13.1	—	—	—	—	—
10.4	5.2	3.3	—	—	—	—	—
11.3	5.4	8.3	—	—	—	—	—
10.6	18.5	4.1	53	1.3	2.9	10.8	29.0
8.7	8.6	4.5	56	1.25	2.7	8.0	18.5
8.2	12.9	4.5	55	1.24	2.8	8.9	21.4
9.5	21.0	4.0	79	1.96	4.4	14.0	18.2
16.3	8.8	2.1	55	2.62	3.4	16.9	35.3
10.3	8.5	13.6	73	.54	.71	2.7	14.3
8.3	3.6	4.3	63	1.45	3.5	9.8	37.1
10.4	22.5	7.7	30	.39	.9	2.4	6.7
13.6	4.9	2.4	92	3.8	4.6	27.0	26.1
11.0	23.0	10.3	98	.96	1.2	6.1	15.0
10.3	13.1	4.6	135	2.9	3.5	21.0	25.7
11.5	4.1	3.4	46	1.35	2.2	8.4	47.8
8.7	14.3	10.0	68	.68	1.1	6.8	23.7
11.7	23.5	3.5	80	2.28	3.6	15.2	18.6
11.3	11.7	2.4	58	2.52	6.0	16.8	21.7
13.5	9.0	8.7	65	.75	1.8	4.8	75.6
10.5	5.9	5.3	92	1.74	3.1	15.1	23.5
—	—	7.2	88	1.22	2.1	9.8	35.7
—	—	5.7	66	1.16	2.0	5.0	54.6
—	—	7.0	60	.86	1.5	5.3	51.8
9.9	14.4	2.2	59	2.68	6.1	16.1	14.6
7.1	6.5	3.2	53	1.65	3.7	11.0	26.0
+2.34	−9.1			−1.34		−8.51	−19.4
−2.0 to +6.8	−17.6 to +0.2			−2.84 to −0.05		−20.9 to +1.5	−30.4 to −10.5
5	5			4		4	4
1.94	3.62			2.68		2.075	5.06
>0.1	<0.02			>0.05		<0.1	<0.01
NS	S			−NS		NS	S

TABLE 2.—(*Continued*)

Myocard. O_2 Ext. Vol. %	*Myocard. O_2 Cons. 100 gm./ml./min.*	*Syst. A-V Vol. %*	*Total O_2 Cons. ml./min.*	*Cardiac Output L./min.*	*Cardiac Index*	*Stroke Volume*	*Per. Res. mm.Hg/L./min.*
10.8	13.1	4.7	—	—	—	—	—
10.0	6.2	8.4	—	—	—	—	—
9.9	12.1	4.0	—	—	—	—	—
12.1	15.6	4.1	159	3.9	6.8	24.4	16.1
10.0	12.9	10.6	93	.87	1.5	4.9	49.0
12.1	15.9	4.6	61	1.3	1.7	8.4	71.4
12.2	14.3	5.6	46	.82	1.1	4.8	72.9
15.2	11.5	5.1	123	2.41	3.2	17.2	32.1
12.4	9.3	6.6	131	1.99	2.7	12.6	22.6
15.1	13.4	5.7	87	1.18	1.9	7.6	65.8
16.7	12.5	7.0	72	1.03	1.7	5.7	47.1
11.2	18.0	3.8	86	2.26	3.8	15.1	32.3
10.9	8.2	7.0	87	1.25	2.1	7.8	25.9
11.2	14.2	3.6	88	2.45	4.1	13.1	41.5
11.1	14.3	4.3	—	—	—	—	—
8.7	6.9	5.1	—	—	—	—	—
6.6	9.9	2.4	47	2.0	3.3	12.5	42.1
5.3	7.8	5.3	42	.80	1.3	4.3	73.0
10.0	9.3	4.6	60	1.3	1.7	8.4	70.6
18.4	9.5	12.1	64	.53	6.7	2.7	78.6
10.7	19.2	3.6	115	3.40	5.5	23.0	20.0
10.3	10.0	9.1	59	.59	.9	3.4	55.6
12.6	10.1	3.7	77	2.10	3.3	14.5	36.4
12.5	9.3	6.8	51	.76	1.2	4.7	45.8
12.4	15.3	4.0	51	1.30	3.0	11.3	30.0
9.9	7.0	7.1	43	.61	1.4	3.5	35.7
9.5	8.7	3.6	76	2.1	2.7	14.0	51.8
15.0	15.0	11.4	65	.57	.8	3.4	11.2
+0.223	−3.49		−17.22	−1.22		−8.96	+4.43
−2.8 to +8.4	−9.8 to +6.3		−66 to +8	−3.03 to −0.15		−19.6 to −1.9	−40.6 to +35.6
12	12		10	10		10	10
2.51	2.11		2.4	2.553		5.1	1.674
<0.05	>0.05		<0.05	<0.05		<0.01	>0.05
S	NS		S	S		S	NS

microspheres suspended in gum acacia had exhibited a significant fall in peripheral vascular resistance ($p<0.01$, Table 1).

Animals injected with microspheres suspended in dog plasma or human albumin showed a significant decrease in myocardial oxygen extraction (0.22 volumes per cent, $p<0.01$, Table 2). pended in plasma or human albumin, all values had returned to control levels (Table 2).

In comparing the circulatory effects in the two series of experiments, it appears that the changes produced using gum acacia as a vehicle were more marked than when dog plasma or human albumin was employed. This

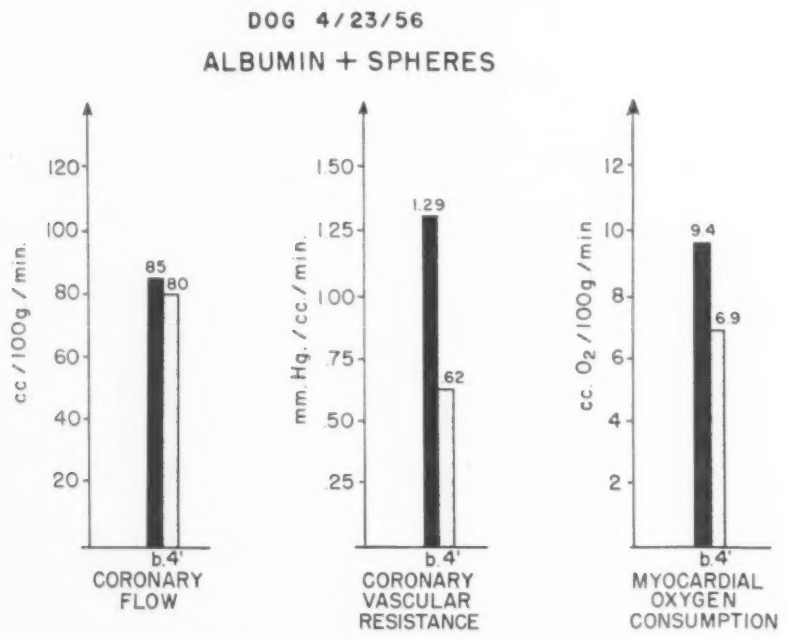


Fig. 1.—The effect of plastic spheres suspended in human albumin on coronary flow, coronary vascular resistance and myocardial oxygen consumption of the dog. It may be seen that there is a slight drop in coronary flow but a marked decline in the coronary vascular resistance, the latter suggesting coronary vasodilatation. The myocardial oxygen consumption decreases because of a fall in the arteriovenous oxygen difference.

The myocardial oxygen usage also decreased (3.49 ml./100 gm./min.); however, this change was not significant ($p>0.05$). In contrast, the injection of microspheres suspended in gum acacia had led to a diminution in the myocardial oxygen usage (Table 1). Twenty-four hours after coronary artery embolization produced by injection of plastic microspheres sus- is particularly true of the changes in mean blood pressure, coronary flow and myocardial oxygen consumption. The significant decrease in coronary vascular resistance seen after coronary arterial embolization produced by the injection of microspheres suspended in dog plasma or human albumin deserves special emphasis (Fig. 1, Table 1).

II. METABOLIC EFFECTS OF CORONARY

TABLE 3.—METABOLIC DATA OBTAINED WITH SPHERES IN GUM ACACIA

Date	*Time*	*Glucose Extraction mg./100 ml.*	*Pyruvate Extraction mg./100 ml.*	*Lactate Extraction mg./100 ml.*	*Ketones Extraction mg./100 ml.*
10–3–55	Control	3.7	.11	1.5	.11
	2 min.	7.3	−.94	−6.4	.24
	1 hr.	1.7	.35	3.0	.04
	3 hrs.	9.5	.06	.5	.72
11–8–55	Control	−1.1	.53	5.1	.18
	2 min.	16.2	−.46	.8	.39
	1 hr.	3.6	1.34	4.9	.23
	2 hrs.	3.1	.79	6.5	.19
	3 hrs.	5.9	.48	6.0	.23
	4 hrs.	3.5	.83	5.4	.50
	5 hrs.	4.3	.51	1.5	.50
11–11–55	Control	4.0	.10	2.8	.07
	2 min.	4.1	−.22	−2.2	.04
	1 hr.	3.6	.32	6.3	.43
	2 hrs.	2.2	.46	2.8	.32
	3 hrs.	3.4	.12	3.3	.36
	4 hrs.	4.7	1.27	6.4	.21
	5 hrs.	3.2	1.07	5.4	.28
11–14–55	Control	1.2	.12	3.7	.17
	2 min.	4.4	.43	3.5	.14
	1 hr.	2.4	.56	6.4	.19
	2 hrs.	2.3	.05	6.7	.50
	3 hrs.	3.7	.17	8.7	.38
	4 hrs.	2.1	.02	6.5	.42
	5 hrs.	1.2	−.68	1.6	.25
11–17–55	Control	2.9	.61	3.9	.25
	2 min.	7.0	.04	2.3	−.46
	1 hr.	4.7	.43	6.7	.26
	2 hrs.	1.2	.14	3.6	3.43
	3 hrs.	2.7	.10	9.2	±0
	4 hrs.	2.9	.16	3.3	.76
	5 hrs.	17.3	.16	7.2	4.07
11–28–55	Control	3.4	.05	6.3	.47
	2 min.	14.9	.20	4.0	.56
	1 hr.	9.1	.53	9.0	.33
	2 hrs.	4.8	.40	6.0	.39
	3 hrs.	3.6	.47	5.7	.65
	4 hrs.	4.0	.18	5.7	±0
	5 hrs.	4.7	.47	6.8	±0
7–20–54	Control	3.3	.07	2.5	.86
	4 min.	11.8	−.07	5.8	−.37
7–28–54	Control	.25	.55	−5.1	.21
	4 min.	4.8	.50	−5.5	.52
10–8–54	Control	6.5	.03	9.5	0.0
	2 min.	5.5	−.05	−4.0	.32
10–12–54	Control	2.7	.01	4.7	.05
	3 min.	25.3	.20	11.5	.33
11–11–54	Control	4.2	.10	7.5	.49
	3 min.	−.33	−.09	−7.8	−.29
11–23–54	Control	.6	.01	1.4	.72
	2 min.	3.7	−.72	−3.7	.12
12–13–54	Control	4.3	0.00	4.9	0.0
	4 min.	5.0	−1.22	1.4	−.07
12–20–54	Control	2.3	.04	3.1	.15
	3 min.	−9.8	−.56	−7.2	−.43
1–6–55	Control	6.2	1.03	9.2	.40
	1 min.	7.6	.05	−5.7	.35
Mean of Difference		+4.2	−0.42	−5.0	−0.19
Range of Observations		−12.1 to +22.6	−1.22 to +0.30	−15.3 to +6.7	−1.23 to +0.32
Degrees of Freedom		14	14	14	14
t		1.935	3.28	3.0	1.528
p		>0.05	<0.01	<0.01	>0.1
Conclusion		S-NS	S	S	NS

ARTERIAL EMBOLIZATION PRODUCED BY INJECTION OF MICROSPHERES SUSPENDED IN GUM ACACIA, DOG PLASMA OR HUMAN ALBUMIN. Table 3 summarizes the effects of coronary arterial embolization in a series of 15 animals on the myocardial extraction of glucose, pyruvate, lactate and ketones with spheres suspended in gum acacia.

Immediately after embolization, the myocardial extraction of glucose showed a rise of 4.2 mg. per 100 ml.; however, this was not significant ($p>0.05$). The myocardial extractions of pyruvate and lactate were significantly diminished (0.42 mg. per 100 ml., $p<0.01$ and 5.0 mg. per 100 ml. and $p<0.01$). The extraction of ketones fell 0.19 mg. per 100 ml. ($p>0.1$, Table 3).

These results were compared to those obtained when spheres were suspended in human albumin or dog plasma (Table 4). The results were qualitatively similar (significant decrease in myocardial extraction of pyruvate and lactate and a not significant increase in myocardial glucose extraction). However, a comparison between Tables 3 and 4 suggests that the metabolic changes described were more severe when gum acacia was used. In addition, the marked rise in arterial lactate concentration, observed following the injection of spheres suspended in gum acacia, was generally not seen when dog plasma or human albumin was employed.

The decreased extraction of pyruvate and lactate observed immediately after coronary artery embolization appeared to be rapidly reversible. Tables 3 and 4 illustrate that in most instances all values had returned to normal after 30 minutes.

It would appear, therefore, that immediately following coronary arterial embolization there occurred a reduction in myocardial extraction of lactate, pyruvate and ketones and a decline in coronary flow. As a result, the myocardial usage of these substrates diminished. As illustrated in Tables 3 and 4, immediately after the injury the concentrations of pyruvate and lactate in coronary vein blood frequently exceeded those in arterial blood (negative myocardial balance). Myocardial glucose extraction and consumption were proportionately less diminished.

III. EFFECTS OF CORONARY ARTERIAL EMBOLIZATION ON PLASMA ENZYME ACTIVITY. Table 5 summarizes the changes observed in plasma activity of malic dehydrogenase, phosphohexose isomerase, fructose aldolase and glutamic oxalacetic transaminase following coronary artery embolization. The average normal values, ranges and standard deviations found for each were as follows (as previously determined): transaminase: 22, 5–37, 9; malic dehydrogenase: 103, 50–170, 47; isomerase: 34, 12–68, 17; aldolase: 46, 24–86, 18[3].

All enzymes showed a marked increase in plasma activity within 2 hours following embolization and reached a peak after 24 hours (Table 5, Fig. 2). Beyond this period there was a rapid decrease of plasma enzyme activity and control levels were generally reached by 72 hours. Similar results were obtained on patients with myocardial infarction (Bing *et al.*[4,5]).

Control animals were treated similarly as the experimental animals, except that human albumin or dog plasma without spheres was injected. The combination of anesthesia and operative procedure produced an increase in plasma enzyme activity after 24 hours but this increase was not as striking as that seen following the injection of the spheres.

IV. GROSS AND HISTOLOGICAL CHANGES IN THE MYOCARDIUM AFTER CORONARY ARTERIAL EMBOLIZATION. a) *Gross*

TABLE 4.—METABOLIC DATA OBTAINED WITH SPHERES AND HUMAN ALBUMEN* DOG PLASMA^

Date	*Time*	*Glucose Extraction mg./100 ml.*	*Pyruvate Extraction mg./100 ml.*	*Lactate Extraction mg./100 ml.*
2-6-56*	Control	—	.14	—
	2 min.	—	−.05	—
	3 hrs.	—	.05	—
	6 hrs.	—	.01	—
	9 hrs.	—	.01	—
	24 hrs.	—	.47	—
	27 hrs.	—	.05	—
	30 hrs.	—	±0	—
4-30-56*	Control	.25	.04	4.16
	2 min.	8.7	−.18	.27
5-9-56*	Control	4.1	.88	6.24
	2 min.	2.3	1.16	7.57
	1 hr.	4.3	1.14	9.98
5-10-56^	Control	3.9	.09	4.82
	2 min.	13.0	.04	2.89
	1 hr.	5.0	.06	7.02
	2 hrs.	−2.9	−.77	6.02
	3 hrs.	3.1	−.43	5.56
5-14-56^	Control	2.2	.59	4.54
	2 min.	6.0	.03	4.07
	10 min.	3.8	.01	2.81
	1 hr.	7.0	.03	1.95
5-15-56^	Control	—	.05	—
	2 min.	—	−.12	—
	10 min.	—	−.21	—
	1 hr.	—	.47	—
5-16-56^	Control	.90	.07	3.56
	2 min.	.30	.29	−6.10
	10 min.	.40	.21	6.92
	1 hr.	3.4	.41	5.20
5-17-56^	Control	—	.05	—
	2 min.	—	−.03	—
	10 min.	—	.48	—
	1 hr.	—	1.08	—
5-18-56^	Control	2.5	−.09	2.78
	2 min.	3.3	−.18	3.16
	10 min.	4.3	—	2.70
	1 hr.	4.3	.18	4.63
5-23-56^	Control	0.0	.08	.08
	2 min.	0.4	−.21	−1.92
	10 min.	0.0	−.13	−.78
	1 hr.	−.2	−.23	.30
5-24-56^	Control	.95	.03	4.63
	2 min.	4.4	±0	−2.02
	10 min.	9.9	.09	1.22
	1 hr.	2.2	.19	1.91
5-24-56^	Control	3.2	.22	4.68
	2 min.	.9	−.04	−2.02
	10 min.	3.4	−.21	1.22
	1 hr.	1.6	.72	1.91
5-25-56^	Control	7.7	.35	5.08
	2 min.	3.4	.23	6.66
	10 min.	1.4	.20	7.79
	1 hr.	3.4	.20	7.04
Degree of Freedom		9	12	9
Mean of Difference		+1.7	−0.155	−3.05
Range of Difference		−4.3 to +9.1	−0.155 to +0.229	−9.66 to +1.58
t		1.205	2.91	2.52
p		>0.05	<0.02	<0.05
Conclusions		NS	S	S

TABLE 5.—AVERAGE LEVELS OF PLASMA TRANSAMINASE, MALIC ACID DEHYDROGENASE, ISOMERASE AND ALDOLASE BEFORE AND AFTER MYOCARDIAL INFARCTION IN DOGS

Hours after Embolization		*0*	*1*	*2*	*3*	*4*	*5*	*24*	*48*	*72*
Transaminase	Average	22 (9)	39 (7)	87 (6)	104 (7)	122 (6)	142 (6)	642 (5)	249 (2)	79 (1)
	Range	5–37	13–110	13–190	25–373	39–245	40–285	70–1388	157–340	—
	Control—1	23	22	—	19	19	—	30	—	—
	Control—2	23	32	31	25	25	—	50	—	—
	Control Average	23	27	31	22	22	—	40	—	—
Malic Acid Dehydrogenase	Average	103 (9)	154 (7)	708 (6)	514 (7)	1015 (6)	1225 (6)	2320 (5)	894 (2)	495 (1)
	Range	50–170	80–280	200–2020	284–1172	420–2590	338–2840	800–6400	580–1208	—
	Control—1	113	177	—	227	—	—	259	—	—
	Control—2	137	270	203	220	310	—	350	—	—
	Control Average	125	224	203	224	310	—	303	—	—
Isomerase	Average	34 (9)	55 (5)	96 (4)	102 (3)	65 (5)	177 (6)	190 (4)	68 (2)	54 (1)
	Range	12–68	21–136	22–296	26–158	23–378	86–438	72–392	32–108	—
	Control—1	54	60	—	—	153	—	123	—	—
	Control—2	16	28	26	25	34	—	42	—	—
	Control Average	35	44	26	25	94	—	88	—	—
Aldolase	Average	46 (9)	54 (7)	72 (7)	64 (7)	58 (7)	100 (6)	419 (5)	228 (2)	82 (1)
	Range	24–86	20–92	23–122	30–123	29–126	45–190	104–749	167–288	—
	Control—1	67	58	—	—	58	—	86	—	—
	Control—2	28	35	35	35	32	—	76	—	—
	Control Average	47	42	35	35	40	—	81	—	—

Figures in parentheses represent number of animals.
Controls 1 and 2 represent observations on animals in which all technical procedures were carried out except for embolization of the coronary arteries.

lesions. When the animals were injected with either gum acacia, dog's plasma or human albumin alone, gross pathological changes were absent. In experimental animals, grossly visible changes at 24 hours were small flame-shaped reddish discolored areas seen through the epicardium. Older infarcts appear as swollen, grayish-yellow discolorations with central softening. The late reparative changes appeared as gray glistening fibrous areas with thinning of the myocardium. The largest lesions measured about 2 cm. in the greatest

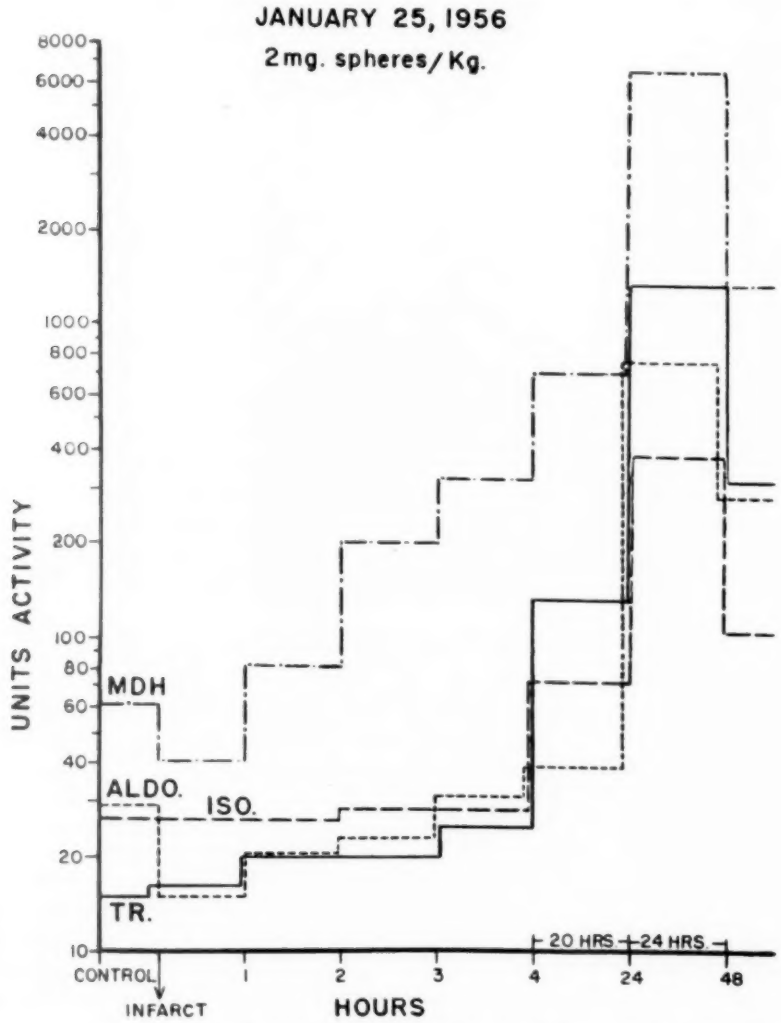


Fig. 2.—Illustrates the effect of injection of plastic spheres in the coronary arteries on plasma enzyme activity of malic acid dehydrogenase, aldolase, isomerase and transaminase in the dog. The rise in plasma enzyme activity occurs approximately 1 to 2 hours after the embolization and the peak of activity is reached 24 hours following embolization. From then on, there is a gradual decline in plasma enzyme activity.

diameter. Areas of infarct were present in both ventricles and atria, with left ventricular changes predominating. A few of the most extensive infarcts reached the epicardium where they were covered by a fibrinous exudate. Occasionally a mural thrombus was found adjacent to the infarcted muscle of necrotic auricular appendage or ventricle. One 24-hour infarct showed extensive gross hemorrhage.

b) *Microscopic findings.* The spheres, when intact, are round and measure about 300 μm. They stain blue with hematoxylin eosin (H&E), orange with Orcein-vanGieson, pale blue or yellow with phosphotungstic acid hematoxylin and are unstained in the other preparations. They lodge in and hyperdistend the medium-sized arteries beneath the epicardium and are seen in the more superficial portions of the myocardium. In many instances these hyperdisdistended arteries show partial to complete mural necrosis and, at times, thrombosis. The thrombi in the necrotic segments are found first distal to the point of obstruction, but later may be found proximal to it (Fig. 3). Apparently necrosis involves only a segment of the circumference of the embolized vessel. These altered segments occasionally show aneurysmal dilatation in a manner reminiscent of periarteritis nodosa.

Ischemic changes are found in all muscle layers of both ventricles and atria in the most severely altered hearts. Though a few of these infarcts are completely transmural, most tend to spare the muscle beneath the endocardium and about the vessels. Many degrees of change may be found, and it should be noted that some of the earlier alterations are present in conjunction with more advanced lesions.

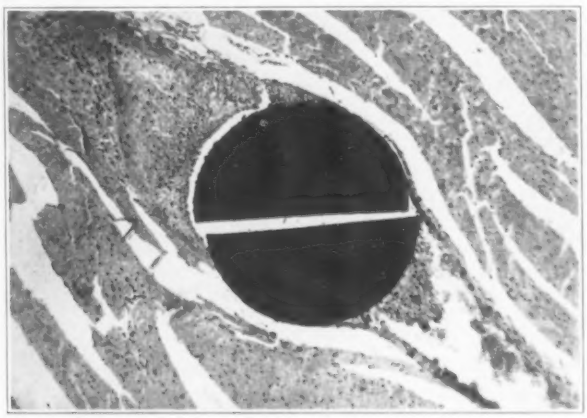


Fig. 3.—Note sphere in hyperdistended artery showing mural necrosis and thrombosis beyond sphere (lower left) 24 hours after embolization. H&E × 100.

Histologic abnormalities in experimental animals will be described in chronological sequence beginning from the time of embolization of coronary arteries. One animal was examined at each time interval after injection of the spheres, except in the 24-hour group where 7 dogs were studied.

The injection of human albumin or the dog's own plasma alone resulted in no pathological alterations. In contrast, gum acacia alone produced definite

changes. Five animals injected with gum acacia alone were sacrificed at 24 hours, except one dog that died earlier. Histologic alterations consisted of occasional minute foci of acidophilic changes of cytoplasm in individual muscle fibers. These changes were less definite than those in the experimental group. Incidental coronary vein thrombosis was found in two animals. Special stains showed minimal but definite alterations in a few instances.

TWENTY MINUTES FOLLOWING EMBOLIZATION. Sections revealed spheres and small foci of coagulative necrosis (increased eosinophilia with loss of cross striations and pyknosis or loss of nuclei on H&E) (Fig. 4). These altered areas show increased PAS coloration on AB–PAS, increase in orange coloration with O–VG but no changes with PTAH or Sudan IV.

THIRTY MINUTES FOLLOWING EMBOLIZATION. Some spheres in branches of the coronary arteries were seen after embolization. There were foci of coagulative necrosis in which some nuclei were pyknotic but none were lost. A few small collections of mononuclear cells, predominantly plasma cells, were found; these obviously antedated this experiment.

FIVE HOURS FOLLOWING EMBOLIZATION. This animal showed no spheres but presented small areas of coagulative necrosis with, for the first time, rare polymorphonuclear leukocytes. Fat stain showed no changes in or about the altered fibers.

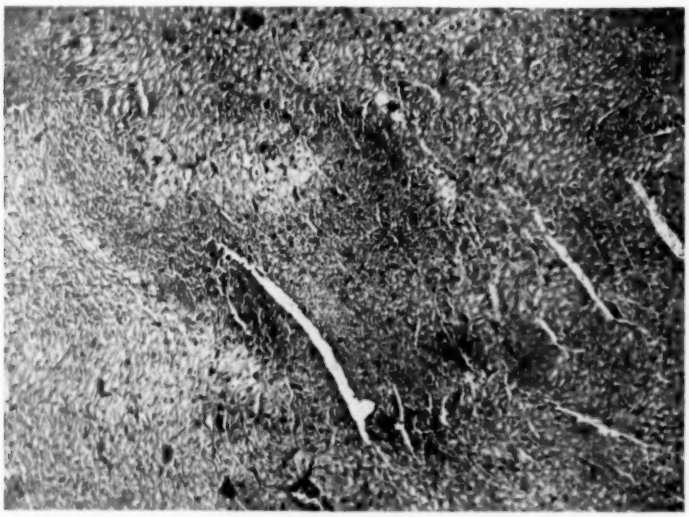


Fig. 4.—Early (20 minute) infarct showing area of coagulative necrosis, center. H&E × 100.

TWENTY-FOUR HOURS FOLLOWING EMBOLIZATION. Of the 7 dogs in this group, four showed more advanced changes and were considered typical. Spheres were found in hyperdistended partially necrotic and thrombosed medium sized arteries. Coagulative necrosis was marked and was associated with a moderate leukocytic infiltration of the infarcted areas (Figs. 5 and 6). These leukocytes tended to concentrate about the periphery of the partially liquefied and necrotic muscle

of the largest lesions, while a few were found in the central portion. There was moderate to marked edema and, in one animal, congestion and hemorrhage. Special stains showed strong PAS coloration of the necrotic arterial segments and of the leukocytes with an increase in glycogen in fibers at the edge of the infarcts. The edematous areas were AB positive and the PTAH showed loss of blue coloration of the infarcted muscle. Sudan IV showed minimal fatty change about the larger infarcts.

TWO DAYS FOLLOWING EMBOLIZATION. Many spheres were found in partially necrotic and thrombosed arteries. A mural thrombus was present which was attached to the endocardium

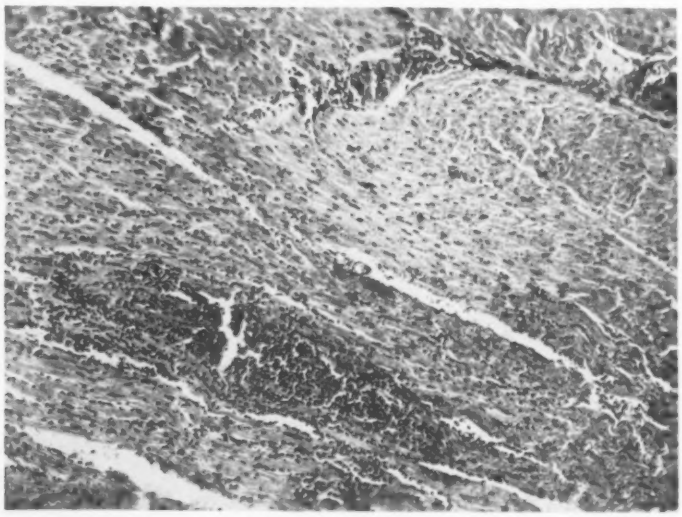


Fig. 5.—Twenty-four-hour infarct showing coagulative necrosis with leukocytic infiltrate. H&E × 100.

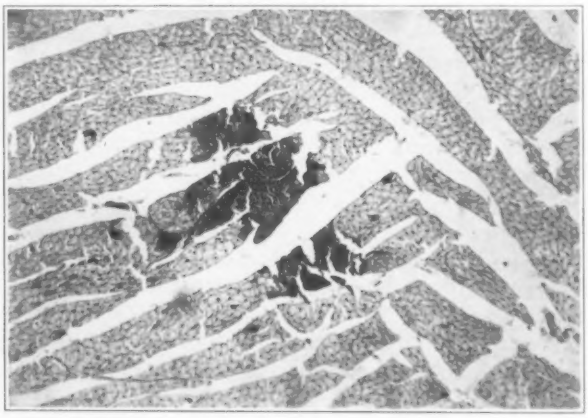


Fig. 6.—Central (PAS positive) area of coagulative necrosis. Twenty-four hours. AB–PAS × 100.

of a partially infarcted left atrium. Coagulative necrosis was extensive but variable in degree with involvement of both endocardium and epicardium. Early proliferation of the larger pale spindle and stellate cells (probably fibroblasts) was found about some of the vessels in the more altered areas (Fig. 7). Leukocytic infiltration was intense especially at the periphery of the infarcted areas. The infarcts showed marked edema and small amounts of fibrin between widely separated and partially resorbed muscle fibers. Special stains demonstrated increase in blue (AB+) colorations in the edematous areas with loss of glycogen in the necrotic muscle.

THREE DAYS FOLLOWING EMBOLIZATION. This animal showed the changes described at 2 days with rather marked liquefaction of the infarcts from which

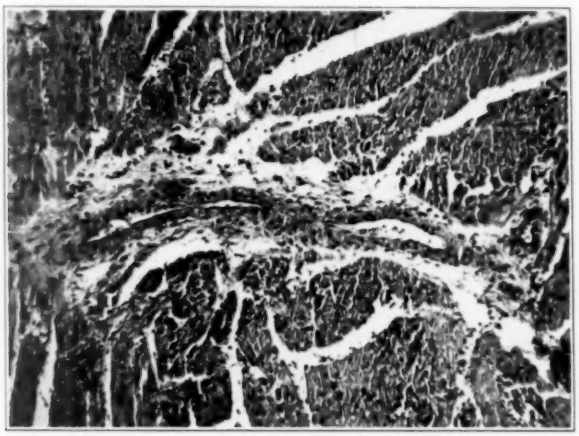


Fig. 7.—Early perivascular proliferation of fibroblasts (spindle shaped cells). Two days. H&E × 100.

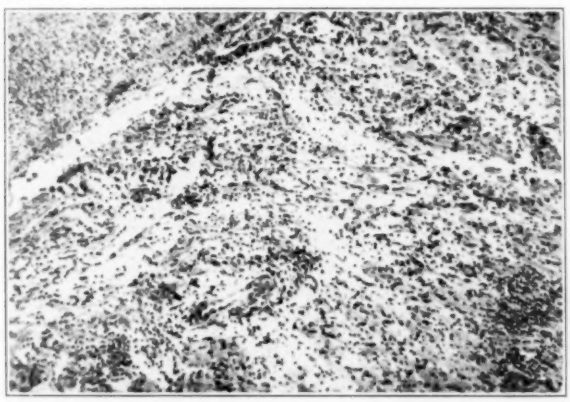


Fig. 8.—More advanced reparative process containing fibroblasts, endothelial cells, leukocytes, phagocytes. Three days after embolization. H&E ×100.

much of the dead muscle had now been removed (Fig. 8). The reparative process was more pronounced.

FOUR DAYS FOLLOWING EMBOLIZATION. The vascular changes were similar to those described above. The areas of coagulative necrosis tended to spare the muscle beneath the endocardium and next to the vessels. Polymorphonuclear reaction was marked about the edges, and in the center of the infarcts. The reparative process had become intensified and an increase in mononuclear cells was evident. Collapse of some of the connective tissue fibers was seen by the O–VG stain where the dead muscle had been removed. Other special stains showed the changes described at 3 days (Fig. 9). The increase in both glycogen and

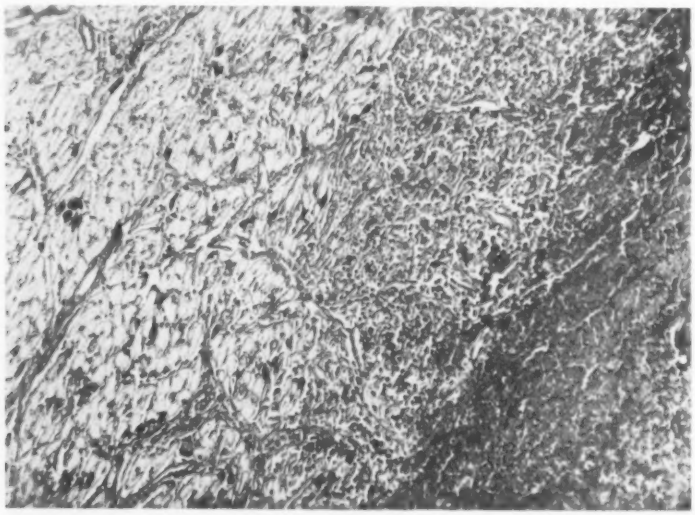


Fig. 9.—Four-day infarct. Edge of area of liquefaction necrosis, lower left. Leukocytes and focal glycogen containing muscle fibers stained. AB–PAS × 100.

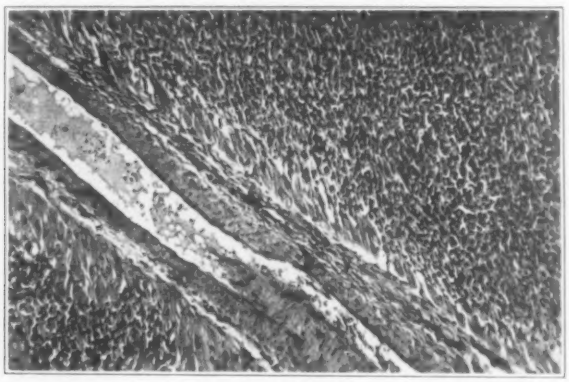


Fig. 10.—Six-day infarct. Note marked cellularity of the reparative process and preservation of muscle about artery. H&E × 100.

fat in the fibers next to the infarctions was marked.

SIX DAYS FOLLOWING EMBOLIZATION. Sections showed spheres in arteries which had undergone hyaline necrosis, some intimal proliferation and thrombosis. Small vessels showed some mural thickening and luminal narrowing. In most areas the necrotic muscle had been removed and was replaced by highly cellular reparative changes. In these areas there were large numbers of fibroblasts, endothelial cells, phagocytes and lymphocytes. Rare polymorphonuclear leukocytes could be found. The cellular areas of repair contained large numbers of basophilic cells with moderate numbers of mitoses and in places almost resembled a malignant tumor (Fig. 10). No additional changes were found with the special stains.

TEN DAYS FOLLOWING EMBOLIZATION. The process was distinctly less

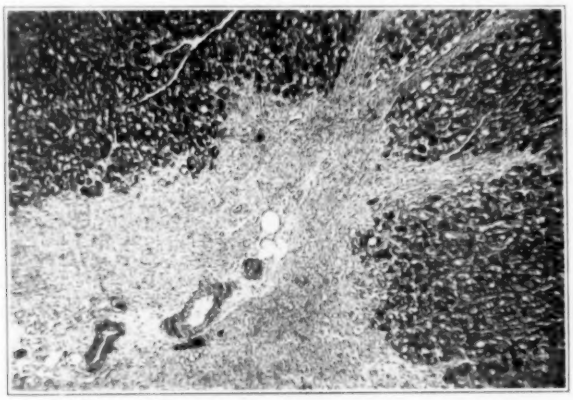


Fig. 11.—Ten-day infarct showing stellate pale staining area of repair with surrounding intact muscle fibers. PTAH × 100.

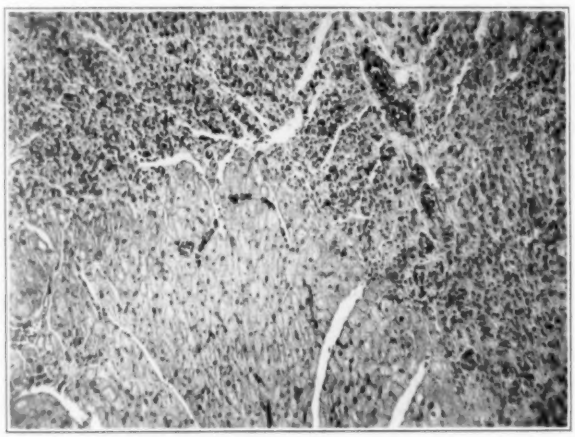


Fig. 12.—Ten-day infarct. Decrease in cellularity of reparative process with maturation of fibroblasts and endothelial cells. H&E × 100.

cellular than in the 6-day animal. The cells showed evidence of maturation with differentiation of the cytoplasm and a decrease in nuclear size and numbers of mitoses (Figs. 11 and 12). More lymphocytes and other mononuclear cells were present in these areas. Collapse of the older framework was seen along with new collagen fibers (O–VG) where the inflammatory changes were least pronounced. AB–PAS showed a marked increase in glycogen about the damaged areas. Some O–VG preparation as bright red acellular tissue which was in sharp contrast to the yellow colorations of the adjacent muscle (Fig. 14). With AB–PAS it displayed both red and blue coloration and with PTAH a pale orange yellow. No new elastic tissue was found.

Discussion. The immediate circulatory alterations that appear following experimental coronary artery embolization are probably due to the short period of decompensation of the myo-

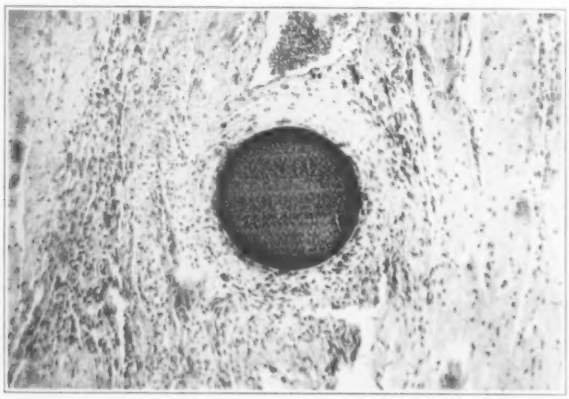


Fig. 13.—Six-week infarct showing firmly embedded sphere representing permanent occlusion. H&E × 100.

of the more altered cells about the margins resembled the "spider cells" of rhabdomyomas.

SIX WEEKS FOLLOWING EMBOLIZATION. Some arteries contained organized fibrotic thrombi while others contained spheres firmly embedded in fibrous tissue (Fig. 13). Small vessels showed mural thickening. Blood pigment and variable numbers of thin-walled capillaries were found in the collapsed loose, fibrillary areas. Collagen formation was generally quite marked, often replacing whole infarcts. The collagen was best seen with the

cardium described by Wiggers[29]. This is the interval during which the heart is in a hypodynamic state[29]. Wiggers[29], Kupfer[17] and Orias[22] have presented evidence that the incomplete ejection in the presence of a relatively unaltered right atrial filling rate results in the rapid increase in left ventricular filling pressure. The remaining functional cardiac tissue responds to this stretch with increased strength of contraction and systolic discharge. If enough uninvolved myocardium is present, compensation can be very rapid and only relatively minor peripheral circulatory alterations

are produced. The period of decompensation immediately following coronary arterial embolization is characterized by a variable decrease in cardiac output, diminished coronary flow, a variable decrease in myocardial oxygen consumption and a proportionate increase in glycolytic activity of the myocardium. There is also coronary vasodilatation, probably of reflex origin.

The injection of microspheres suspended in gum acacia results in no significant change in coronary vascular resistance, since mean blood pressure and coronary flow decline proportionately. It appears that gum acacia solution, due to its high viscosity, is responsible for the marked decrease in flow and probably masks any coronary vasodilatation that occurred when a less viscous solution is injected. Thus when dog plasma or human albumin is used as the vehicle for the injected microspheres, the viscosity effect is small and the fall in coronary vascular resistance observed might well be ascribed to actual changes in the caliber of coronary arterioles, possibly of reflex origin.

In the series of animals injected with spheres suspended in plasma, the oxygen usage by the myocardium remains essentially unchanged. However, when gum acacia is used, the myocardial oxygen usage is significantly reduced. This may account for the fact that the metabolic changes in animals injected with spheres suspended in gum acacia are quantitatively more severe. These alterations in myocardial metabolism, that is, decreased myocardial usage of pyruvate and lactate in the presence of an unaltered myocardial glucose consumption, suggest that in the brief period following embolization glucose may be the primary metabolite. Certainly the fact that pyruvate and lactate concentrations in coronary vein blood exceed those in arterial blood (negative extraction of pyruvate and lactate) is further evidence of incomplete oxidation of carbohydrates. The observation

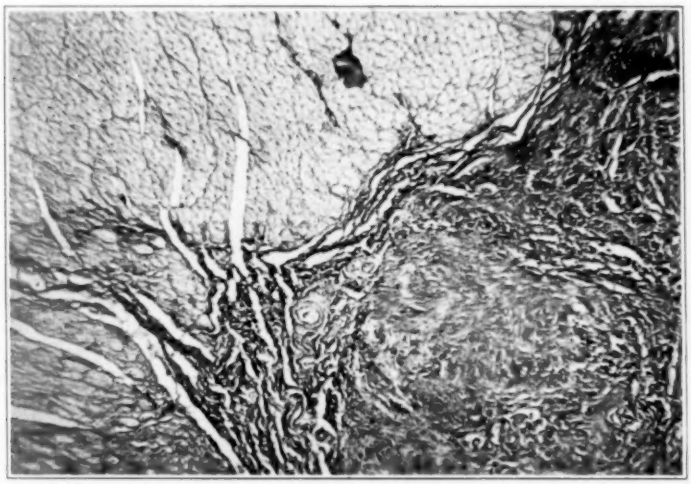


Fig. 14.—Six-week infarct. Note dense collagen scar in left lower field. O–VG × 100.

that myocardial usage of glucose is less affected than that of pyruvate and lactate is probably due to the fact that anaerobic glycolysis can still proceed in heart muscle under these conditions.

While these rapidly reversible circulatory and metabolic changes are present only during the period of cardiac depression, the changes in plasma enzyme activity are associated with pathological events that take place many hours following coronary arterial embolization. Thus the peak of plasma enzyme activity occurs 24 hours after embolization and is correlated with the height of coagulation necrosis of the myocardium. Enzymes released into the blood from the injured tissue decrease as regenerative processes take place.

Pathological observations demonstrate that the changes observed in the animals of this series are similar to those described in the dog by Karsner[16]. The first changes consist of microscopic alterations with increased eosinophilia, loss of cross striation with pyknosis, or disappearance of nuclei (coagulative necrosis). Then polymorphonuclear infiltration is seen, which becomes pronounced in 2 or 3 days, when it is accompanied by liquefaction necrosis, by resorption of dead muscle fibers and by condensation of the leukocytes about the infarcted areas. About this time fibroblasts appear about small vessels. This is followed by diminution in leukocytes and increase in fibroblasts and other mononuclear cells. The reparative process is most marked at 6 days. The cellularity then diminishes by the tenth day and fibroblasts and endothelial cells show maturation. Early collagen formation appears in the areas of more advanced repair. At 6 weeks cellular reaction has disappeared, to be replaced by loose fibrillary tissue or by acellular collagen. No foreign body giant cell reaction and no plasma cells are found. Furthermore, no new elastic fibers or regeneration of muscle have been noticed. Although the pathological events follow in general the sequence outlined above, many animals show simultaneously occurring stages of tissue injury and repair. This is probably the result of new infarcts resulting from propagation of older thrombi forming next to spheres.

Except for the time factor, the entire process is comparable to that found in human myocardial infarction. Changes encountered in this experimental series progress more rapidly. It is possible that this is the result of the small size of the experimental infarct, and the relatively greater metabolic rate which exists in smaller animals per unit of tissue[27]. Similar to human infarctions, the experimental lesions are associated with a high concentration of fat and glycogen in the altered muscle at the edge of the infarcts. Another comparable feature is the tendency to spare the muscle just beneath the endocardium and about the vessels.

In reviewing the circulatory, pathologic and biochemical findings reported in this paper, it appears that the factor which initiates the sequence of events is myocardial ischemia produced by mechanical blockage of some of the coronary vessels. The localized response to this injury appears to be coronary vasodilatation as a result of an intercoronary reflex or of accumulation of anaerobic metabolites. The localized myocardial ischemia results in a period of decompensation of the affected heart muscle with a decrease in cardiac output and blood pressure. These changes appear rapidly reversible because of compensatory mechanisms (Wiggers[29]). Localized myocardial ischemia leads to immediate though fleeting changes in utilization of substrates by the heart. There is a proportionate increase in anaerobic activity of heart muscle. Myocardial usage of py-

ruvate and lactate diminishes, with myocardial glucose usage being less affected. Immediately following these early chemical alterations, the heart muscle shows beginning coagulative necrosis, suggesting that these metabolic changes have led to cell death. The height of cell necrosis, observed 24 hours following the injury, coincides with the peak of plasma enzyme activity. As reparative processes in heart muscle proceed, the plasma enzyme activity declines.

Summary. The circulatory, metabolic and pathologic sequelae of experimental coronary infarction produced by the injection of plastic spheres were investigated.

Intracoronary injection of spheres suspended in gum acacia, human albumin or dog's plasma resulted in decreased cardiac output, diminished coronary flow and myocardial oxygen consumption. These changes were more severe when gum acacia was used as the vehicle for the spheres. The injection of microspheres suspended in human albumin or dog's plasma led to coronary vasodilatation, possibly of reflex origin.

Immediately following coronary artery embolization, there occurred a reduction in myocardial extraction and usage of lactate, pyruvate and ketones. Myocardial glucose extraction and consumption were proportionately less diminished. These changes appeared to be rapidly reversible.

Plasma activity of malic dehydrogenase, phosphohexose isomerase, fructose aldolase and glutamic oxalacetic transaminase rose within 2 hours following embolization and reached a peak after 24 hours.

Pathologic observations consisted of early coagulation necrosis followed by polymorphonuclear infiltration, repair (increase in mononuclear cells) and collagen formation.

A correlation of the data indicates that localized myocardial ischemia led to a period of mechanical decompensation of the heart, accompanied by fleeting changes in utilization of substrates. Immediately following the chemical alterations, there was coagulation necrosis, the height of which coincided with the peak of plasma enzyme activity. As reparative processes in heart muscle took place, plasma enzyme activity declined.

REFERENCES

1. **Agress, C. M., Rosenberg, M. J., Jacobs, H. I., Binder, M. H., Schneidermann, M. H.,** and **Clark, W. G.:** Am. J. Physiol., **70,** 536, 1952.
2. **Barker, S. B.,** and **Summerson, W. H.:** J. Biol. Chem., **138,** 535, 1941.
3. **Bing, R. J.:** Harvey Lectures, Series L. New York: Academic Press, Inc., 1954–1955.
4. **Bing, R. J., Castellanos, A., Gradel, E., Siegel, A.,** and **Lupton, C.:** Tr. Assn. Am. Phys., **69,** 170, 1956.
5. **Bing, R. J., Castellanos, A.,** and **Siegel, A.:** The diagnostic value of plasma activity of malic acid dehydrogenase and phosphohexose isomerase in patients with myocardial infarction and liver disease. In preparation.
6. **Bing, R. J., Hammond, M., Handelsman, J. C., Powers, S. R., Spencer, F., Eckenhoff, J. B., Goodale, W. T., Hafkenschiel, J.,** and **Kety, S. S.:** Am. Heart J., **38,** 1, 1949.
7. **Bodansky, O.:** Cancer, **7,** 1191, 1954.
8. **Bruns, F.:** Biochem. Ztschr., **352,** 156, 1954.
9. **Engel, F.:** Personal communication, 1952.
10. **Fick, A.:** Sitzung. phys. med. Gesell. zu Wurzburg, July, 1870, p. 16.
11. **Friedemann, T. E.,** and **Haugen, G. E.:** J. Biol. Chem., **147,** 415, 1943.
12. **Gilbert, R. P., Goldberg, M.,** and **Griffin, F.:** Circulation, **9,** 847, 1954.
13. **Greenberg, L. A.,** and **Lester, D.:** J. Biol. Chem., **154,** 177, 1944.
14. **Hagedorn, H. C.,** and **Jensen, B. N.:** Biochem. Ztschr., **135,** 46, 1923.

15. **Karmen, A., Wroblewski, F.,** and **LaDue, J. S.:** J. Clin. Invest., **34**, 126, 1955.
16. **Karsner, N.,** and **Dwyer, O.:** J. Med. Res., **34**, 21, 1916.
17. **Kupfer, S.:** Proc. Soc. Exper. Biol. & Med., **76**, 134, 1951.
18. **Lacey, O.:** Statistical Methods in Experimentation: An Introduction. New York: The Macmillan Co., 1953.
19. **Mallory, G. K., White, P. D.,** and **Salcedo-Salgar, J.:** Am. Heart J., **18**, 647, 1939.
20. **McManus, J. F. A.:** Stain Technol., **23**, 99, 1948.
21. **Mowry, W. B.:** Personal communication, 1956.
22. **Orias, O.:** Am. J. Physiol., **100**, 629, 1932.
23. **Scholander, P. F.:** J. Biol. Chem., **167**, 235, 1947.
24. **Siegel, A.,** and **Bing, R. J.:** Proc. Soc. Exper. Biol. & Med., **91**, 604, 1956.
25. **Smith, W. W., Wikler, M. S.,** and **Fox, A. C.:** Circulation, **9**, 352, 1954.
26. **Somogyi, M.:** J. Biol. Chem., **86**, 655, 1930.
27. **Spencer, F. C., Merrill, D. L., Powers, S. R.,** and **Bing, R. J.:** Am. J. Physiol., **160**, 149, 1950.
28. **Van Slyke, D. D.,** and **Neill, J. M.:** J. Biol. Chem., **61**, 523, 1924.
29. **Wiggers, C. J.:** Ann. Int. Med., **23**, 158, 1945.

SUMMARIO IN INTERLINGUA

Infarcimento Myocardial Experimental: Alterationes Circulatori, Biochimic, e Pathologic

Le presente studio correlationa le consequentias circulatori, biochimic, e pathologic del occlusion coronari experimental resultante del injection intracoronari de microspheras de plastico. Le immediate alterationes circulatori consisteva in breve reductiones del rendimento cardiac, del fluxo coronari, e del pression de sanguine. Le resistentia vascular coronari se abassava. Le alterationes metabolic esseva transiente e revelava un augmento proportional del metabolismo anaerobe del corde. Le alterationes esseva reinfortiate quando le spheras esseva suspendite in un medio a alte grado de viscositate (acacia). Le activitate plasmatic de dishydrogenase malic, phosphohexosa-isomerase, transaminase glutamic oxalacetic, e fructosa-aldolase attingeva su culmine 24 horas post le infarcimento. Le embolisation esseva sequite per necrose coagulational, infiltration leucocytic, e reparo de histos.

Un correlation del datos indica que localisate ischemia myocardial resultava in un periodo de discompensation mechanic del corde, accompaniate per transiente alterationes in le utilisation de substratos. Immediatemente post le alterationes chimic il occurreva necrose coagulational, coincidente in su culmine con le culmine del activitate enzymatic in le plasma. In tanto que processos reparatori del musculo cardiac occurreva, le activitate enzymatic in le plasma se reduceva.

INCIDENCE OF COEXISTENT ESSENTIAL HYPERTENSION AND MALIGNANT NEOPLASTIC DISEASES

STUDY BASED ON RECORDS OF 509 CLINIC PATIENTS WITH AND 509 WITHOUT MALIGNANT NEOPLASMS

By Phillip J. Moore, M.D.*
FORMER FELLOW IN DIVISION OF MEDICINE

R. D. Taylor, M.D.**
FORMER MEMBER OF STAFF, RESEARCH DIVISION

AND

A. C. Corcoran, M.D.

(From the Division of Research, The Cleveland Clinic Foundation and The Frank E. Bunts Educational Institute, Cleveland, Ohio)

Hypertensive and neoplastic diseases are common in late adult life. In the age group 40 through 59 years, about one person in 10 shows hypertensive levels of diastolic arterial pressure in casual readings (Master, Garfield and Walters[9]), and about one in 50 dies of a malignant neoplasm. It would be anticipated that the two conditions which usually develop in adults would occur together less often than they would occur singly, if only because the one might prove fatal before the other became manifest. However, many internists, ourselves among them, have shared the view that patients with neoplastic lesions infrequently show evidences of hypertensive disease and *vice versa*.

Surveys made during the past 10 years have tended to support this impression (Foldes[4], Jacobson[6], Wanscher, Clemmesen and Nielsen[11], Zondek[13,14], and Zondek and Tchelchik[15]). But these data have been variously collected from death certificates (Jacobson[6]), or from necropsy (Wanscher, Clemmesen and Nielsen[11]), or clinical records (Foldes[4], Zondek[13,14], and Zondek and Tchelchik[15]), and have been based on varying criteria. No attempt has been made to segregate essential hypertension (Page and Corcoran[10]) from the transient hypertensions or from increases in systolic pressure common in older age groups, and allowance has not been made for the hypotensive effects of wasting disease. Hence the available information is inconclusive.

The present study was aimed at a more precise definition of the association or lack of association between neoplastic diseases and hypertensive disease having the characteristics of essential hypertension. Observations were made in two groups of Clinic patients of like age (40 through 59 years) and sex distribution. The one group consisted of patients whose records showed that they had developed malignant neoplasms. The second, or control group was selected by serial study of charts of patients apparently free of neoplastic disease, matching this group with the neoplastic group in

*Present address: The Owosso Medical Group, 113 East Williams Street, Owosso, Michigan.
**Present address: The Medical Center, Marshfield, Wisconsin.

age and sex distribution. Records of each group were then searched for evidences of essential hypertension, using criteria listed below.

The data obtained indicate that, in the groups studied, hypertensive disease is indeed relatively uncommon in patients with neoplastic disease. Statistical considerations (Berkson[1,2,3] and Mainland[8]), indicate that datum such as this, bearing on the association of two diseases and based either on necropsy or clinic records, does not have pathogenetic significance, unless it can be supported by further studies. However, since the differences observed in the incidences of essential hypertension between control and neoplastic groups are large, and since the study involves stricter criteria of hypertensive disease than those previously used, the results are reported with the major aim of stimulating further, more conclusive study of this association.

Procedure. The survey was begun by review of 509 charts of patients aged 40 through 59 years, all of whom at some time, although not necessarily while in this age group, had manifested histopathologically proven malignant neoplasms. This term was used to include carcinomas, sarcomas and the leukemias; records indicating that the tumors were of borderline malignancy were excluded from the group.

Since the effects of fever, cachexia and wasting disease may mask the presence of pre-existing hypertension, no chart was included in the study group which did not indicate that, at the time the blood pressure was measured, the patient was ambulatory and in such condition as to undergo necessary examination as an outpatient.

Criteria for the diagnosis of essential hypertension were necessarily arbitrary. The usual basis for this diagnosis was the finding of elevated diastolic arterial pressure of 100 mm. Hg or more on 3 successive Clinic visits and in the absence of signs of renal, endocrine or other definable cause of secondary hypertension (Page and Corcoran[10]). When this degree of hypertension was recorded at only one or two examinations, the chart was included in the study only if the diagnosis of essential hypertension could be supported by cardiac or ocular fundal examination. Single determinations of diastolic pressure at levels less than 100 mm. Hg were accepted for classification of the record in the normotensive group.

Results. The incidences of essential hypertension in neoplastic and control groups, segregated by sex and subgrouped by age classes, are listed in Table 1. In both sexes and in the two decades surveyed, essential hypertension was less common in the neoplastic group than in the control group. The difference is more striking in men ($P = .0001$) than in women ($P = .01$). This was because hypertension, although still less frequent than in the controls of 50 through 59 years, was much more common in women than in men of this age. The difference in incidence of hypertension in this age class between the neoplastic group and the control group is of only dubious statistical significance ($P = .2$); however the direction of this difference is the same as in the other classes and this uniform trend indicates that the difference is significant. Table 2 lists, among the neoplastic group, the sites of the lesions, the numbers of patients with lesions at each site who were listed as normotensive and, in parentheses, those listed as hypertensive; the data again demonstrate the greater frequency of hypertension in women than in men with neoplastic disease.

Discussion. The criteria for the diagnosis of essential hypertension were arbitrary and deliberately rigid, since the aim was to limit the study to this specific condition. The diastolic pressure of 100 mm. Hg level chosen as the primary criterion is at or about the upper limit of the normal range of pressures as recently redefined for this age class by Master, Garfield and Walters[9]. The insistence of repeated measurements at this level, or on systemic evidence of sustained hypertension was

aimed at excluding patients who showed only transient increases of diastolic pressure. Many patients with transient hypertension do show an increased incidence of subsequent persistent hypertension (Levy *et al.*[7]) but some do not, so that it would be inaccurate to equate transient with essential hypertension. Exclusion from consideration of systolic pressure was done with the aim of limiting the diagnostic area to essential hypertension. Systolic hypertension is a common, relatively benign consequence of aortic arteriosclerosis in patients of 50 and more years and is hemodynamically and etiologically distinct from essential hypertension.

Using these criteria, we have obtained more precise evidence than has been available of the dissociation between malignant neoplastic disease and hypertension. Jacobson[6], using death certificate data, which are notoriously lacking in uniformity, had previously shown that cancer and cardiovascular-renal disease tended to occur together less often than cancer and diabetes

TABLE 1.—INCIDENCE OF ESSENTIAL HYPERTENSION IN 509 CASES OF MALIGNANT NEOPLASMS AND IN 509 CONTROLS

Sex and Age Range (years)	*Neoplastic Cases*			*Controls*				
	Total No.	*Hypertension No.*	*%*	*Total No.*	*Hypertension No.*	*%*	*S.E.D.**	*P***
MEN								
40–49	75	0	0	75	7	9.3	±3.5	.0033
50–59	202	2	1	202	17	8.4	±2.1	.0044
40–59	277	2	0.7	277	24	8.7	±1.8	.0001
WOMEN								
40–49	88	0	0	88	10	11.4	±3.5	.0010
50–59	144	15	10.4	144	22	15.3	±4.9	.22
40–59	232	15	6.5	232	32	13.8	±2.8	.01

* Standard error of the difference of means (Hill[8]).
** Probability of chance occurrence of the observed difference in incidence between neoplastic and control group.

TABLE 2.—ANALYSIS OF 509 CASES OF MALIGNANT NEOPLASM

	Number of Patients			
	Men		*Women*	
Site or Type of Neoplasm	*40–49**	*50–59**	*40–49**	*50–59**
Gastrointestinal tract	23	69	17	32 (2)**
Respiratory tract	12	57	6	12 (5)
Skin	9	14	9	14 (2)
Genitals	6	11	21	25
Breast	0	0	20	29 (4)
Urinary tract	6	20	2	6 (1)
Central nervous system	7	4	4	6
Endocrines	2	4 (1)	3	3
Primary unknown	2	3	0	2
Leukemias, sarcoma	8	20 (1)	6	15 (1)
Totals	75	202 (2)	88	144 (15)

* Age when observed for essential hypertension.
** ( ) Cases with essential hypertension.

mellitus, cancer and tuberculosis, or cancer and syphilis. Foldes[4] from 68 office records of cancer patients and a like number of patients without cancer came to the conclusion that hypertension and coronary artery disease were infrequent in patients with cancer. Wanscher, Clemmesen and Nielsen[11] found, at necropsy, less atheroma in cancer patients than in controls without cancer; this result would be anticipated, since wasting disease tends to remove atheromatous deposits (Wilens[12]). Zondek[13] used 150/90 as the limits of normotension and studied patients older than 40 years, so that he would include in the category of hypertension both essential hypertension and systolic arteriosclerotic hypertension. Even with this difference in definition, his data, which like ours have been extended to include leukemia and sarcoma (Zondek[14], and Zondek and Tchelchik[15]), demonstrate less hypertension in patients with neoplastic disease than in controls of the same ages and also show that the difference is greater in men than in women.

What can we conclude from the array of evidence? From our data, only the fact that, in Clinic patients, diastolic hypertension of the type associated with essential hypertension is about one-twelfth as common in men and about one-half as common in women with neoplastic disease as it is in control groups of like age and sex who have no evidences of neoplasia. This relative incidence might be an artifact, attributable to weighting of the control group with disproportionate numbers of patients with hypertensive disease. That this is not the case can be shown by reference to control groups calculated from the data of Master, Garfield and Walters[9] from their data on industrial workers. Calculations based on their data, assuming the age and sex distribution of our neoplastic group, indicate incidences of hypertension of 9% in men and 10% in women. These calculated incidences contrast with the observed values of 1 and 6%, respectively, in our neoplastic cases. Thus, the indicated low incidence of hypertension in patients with neoplastic disease persists when the standard of reference is a working population rather than a clinic group, and is apparently not artifactual.

Nevertheless, no definitive pathogenetic significance can be attributed to this fact; this would require broad epidemiologic study of presumably normal populations and laboratory experiment. ". . . in science there is no substitute for experiments. It is a central purpose of this essay to urge that an adequate program of experimentation with animals be accomplished before definitive conclusions are drawn. . . ." thus Berkson[3] in his evaluation of data on the relation between smoking and lung cancer. Berkson has reminded us in an informal personal communication[2] of the relevance of this statement to the present data, and to similar, less conclusive previous studies.

Summary and Conclusions. 1) The incidences of essential hypertension (defined primarily from diastolic pressures of 100 mm. Hg or more) were determined records of 509 Clinic patients with malignant neoplasms and in 509 records of controls without neoplastic disease, matched for the distributions of sex and age. Hypertension was less common in men than in women in the neoplastic series and in both was less common than in the non-neoplastic control group. This finding agrees with previous studies, in which hypertension was less strictly defined.

2) No definitive pathogenetic implication can be ascribed to this fact. A relatively low incidence of hyperten-

sion in patients with neoplastic disease persists when the reference standard is a working population, rather than a clinic group, so that this low incidence of hypertension may have further significance. This can only be elucidated by epidemiologic and, as techniques permit, experimental study in animals of the association between hypertensive and neoplastic disease.

ADDENDUM. In a paper which came to our attention after completion of this manuscript, **S. G. Zondek** (Acta med. scandinav., **152**, 231, 1955) has reported further data on the dissociation between hypertension and malignant growth, demonstrating that this tendency is more manifest in men than in women and that hypertension and rheumatoid arthritis also show a dissociation in incidence. From this, he speculates that the agent which causes hypertension is antiproliferative and anti-inflammatory as well as pressor and that an agent such as cortisone would have these properties.

REFERENCES

1. **Berkson, J.**: Biometrics Bull., **2**, 47, 1946.
2. Idem: Personal communication.
3. Idem: Proc. Staff Meet., Mayo Clin., **30**, 319, 1955.
4. **Foldes, E.**: New York State J. Med., **49**, 1, 1949.
5. **Hill, A. B.**: Principles of Medical Statistics. 6th ed. New York: Oxford University Press, 1955.
6. **Jacobson, P. H.**: Milbank Mem. Fund Quart., **26**, 90, 1948.
7. **Levy, R. L., White, P. D., Stroud, W. D.,** and **Hillman, C. C.**: J. Am. Med. Assn., **135**, 77, 1947.
8. **Mainland, D.**: Am. Heart J., **45**, 644, 1953.
9. **Master, A. M., Garfield, C. I.,** and **Walters, M. B.**: Normal Blood Pressure and Hypertension: New Definitions. Philadelphia: Lea & Febiger, 1952.
10. **Page, I. H.,** and **Corcoran, A. C.**: Arterial Hypertension: Its Diagnosis and Treatment. 2nd ed. Chicago: Year Book Publishers, Inc., 1949.
11. **Wanscher, O., Clemmesen, J.,** and **Nielsen, A.**: Brit. J. Cancer, **5**, 172, 1951.
12. **Wilens, S. L.**: A.M.A. Arch. Int. Med., **79**, 129, 1947.
13. **Zondek, S. G.**: Brit. J. Cancer, **6**, 131, 1952.
14. Idem: Harefuah (J. Med. Assn., Israel), **44**, 73, 1953.
15. **Zondek, S. G.,** and **Tchelchik, M.**: Brit. J. Cancer, **7**, 418, 1953.

(Interlingua on page 600)

SPINAL FLUID ALCOHOL IN YEAST MENINGITIS

By Richard Tyler, M.D.

(From the Peter Bent Brigham Hospital; the Neurological Unit of the Boston City Hospital; and the Department of Neurology, Harvard Medical School, Boston, Massachusetts)

It is well known that the cerebrospinal fluid sugar frequently falls in cases of cryptococcal meningitis. Since yeast and bacterial sugar metabolism have different end products, it was considered worthwhile to try to determine whether the theoretical end products of yeast metabolism could be tested for. Such a test would be of value to the clinician as it would provide a chemical way of differentiating between the two types of meningitis and possibly suggest the need for appropriate bacteriological studies. Its greatest value would be in those cases of lymphocytic meningitis where no organism had been found.

Werkman and Wood (1942)[2] have pointed out that yeasts, of which cryptococcus represents a typical example, utilize glucose for energy; and the final metabolic stage of glucose metabolism in anaerobic media is decarboxylation of pyruvate to acetaldehyde and then conversion to ethyl alcohol. This end product is not found after anaerobic bacterial degradation of sugar.

Material and Method. For the determination of alcohol the technique of Niclaux[1] was chosen. The method is only semiqualitative in that it measures all substances that are oxidized by potassium dichromate. In spinal fluid, for all practical purposes, only alcohol will give a positive result.

The test was performed by adding 1.0 ml. of a saturated solution of potassium dichromate in concentrated sulfuric acid to 1.0 ml. of spinal fluid. Tests were read at 5 minutes, 2 hours, and 24 hours. The latter specimens showed increasing differentiation between color in the control and the test specimen. The presence of a green color was taken as an indication that the potassium dichromate was reduced, and, thus, that alcohol had been present in the cerebrospinal fluid.

Two hundred random spinal fluids that were sent to the laboratory for routine testing were used as controls. Three cases of pneumococcal, 4 cases of meningococcal, and 6 cases of tuberculous meningitis were used as examples of bacterial meningitis, and spinal fluid from 5 cases of cryptococcal meningitis were used as examples of yeast meningitis.

Results. There were 5 samples of spinal fluid from cases of cryptococcal meningitis. Three of these had abnormally low sugars, and all 3 gave strongly positive tests. The 2 spinal fluids with sugars within the normal range produced negative or equivocal results.

In all the cases of bacterial meningitis the results were negative despite low sugar levels.

There was a positive reaction in only one of the 200 control spinal fluids. This patient came in because of status epilepticus and received large doses of paraldehyde 2 hours before the spinal tap. A repeat examination 24 hours later gave a negative result. In this case, I believe, there was a positive result because of a significant level of paraldehyde in the spinal fluid (and since this is an aldehyde it is quite capable of being reduced by potassium dichromate). The level of sugar in this spinal fluid was normal on both examinations.

It should also be noted that after the addition of the $K_2Cr_2O_4$–H_2SO_4 mixture, the spinal fluid of some patients with cryptococcal meningitis showed a precipitate, which is being investigated further. This was not noted

in the control or bacterial meningitis fluids.

Discussion. The testing of the spinal fluid for the presence of alcohol seems to offer, theoretically and practically, a useful adjunct to the clinician's armamentarium. It utilizes the knowledge of glucose metabolism, which in bacterial metabolism results in end products of acetic and fumic acid (and often small amounts of lactic acid, acetyl methylcarbonal, and CO_2)[2] and in yeast-alcohol. Since the former are not readily oxidized by $K_2Cr_2O_4$ and the latter are, under the test conditions differentiation appears to be theoretically easy.

In practice it is seen that spinal fluid of only 3 of the 5 cases of cryptococcal meningitis did reduce the solution. These were the 3 cases that had a low sugar. Therefore, it would seem that a positive test is strong presumptive evidence of a yeast meningitis and can be expected in the presence of a low sugar, but the presence of a high sugar suggests that metabolism is not sufficiently rapid for enough end products to have accumulated to give a positive test.

We did not have any spinal fluid from patients with coccidioidal meningitis, but we would anticipate this would give a positive test.

Summary. A method of distinguishing yeast meningitides from bacterial meningitides is proposed, and a demonstration of its practical application is reported. In 3 out of 5 cases of cryptococcal meningitis a significant amount of cerebrospinal fluid alcohol was found. No significant amount of alcohol was found in any case of meningococcal, tuberculous, pneumococcal, or influenzal meningitis.

REFERENCES

1. **Niclaux, M.:** Cited by **Schweisheimer, W.:** Deutsches Arch. f. klin. Med., **109**, 272, 1913.
2. **Werkman, C. H.,** and **Wood, H. G.:** Advances in Enzymology. **2**, 135–182 New York: Interscience Publishers, 1942.

SUMMARIO IN INTERLINGUA

Alcohol del Fluido Spinal in Meningitis Mycotic

Es proponite un methodo de distinguer inter meningites mycotic e meningites bacterial, e es reportate un demonstration de su application practic. In 3 inter 5 casos de meningitis cryptococcic esseva trovate un quantitate significative de alcohol in le fluido cerebrospinal. Nulle quantitate significative de alcohol esseva trovate in ulle caso de meningitis meningococcic, tuberculotic, pneumococcic, o influenzal.

THE EFFECT OF HYALURONIDASE ON THE ABSORPTION OF SUBCUTANEOUSLY ADMINISTERED PHENOL RED*

By Eugene A. DeFelice, M.D.
CIBA FELLOW IN PHARMACOLOGY

R. Richterich-van Baerle, M.D.
INSTRUCTOR IN PHARMACOLOGY

Robert Megirian, M.S.

AND

Earl H. Dearborn, Ph.D., M.D.
PROFESSOR OF PHARMACOLOGY

(From the Department of Pharmacology, Boston University School of Medicine, Boston, Massachusetts)

Phenol red excretion has been used extensively as a kidney function test and for the study of permeability or absorption. In spite of much clinical and investigative work with this drug, only incomplete studies of its excretion after administration by different parenteral routes could be found. That such a study might be valuable is indicated by the following. For the evaluation of kidney function, phenol red is injected intravenously or intramuscularly. After intramuscular administration a time allowance of 10 minutes is usually made to compensate for the slower rate of absorption. We have not been able to find any published basis for this assumption; furthermore, it is hardly reasonable that the same values be considered "normal" after intravenous as after intramuscular injection.

During the last five years numerous studies have suggested that the intravenous injection of antibiotics, anticoagulants, contrast media for pyelography, and other drugs could be replaced by subcutaneous injection if hyaluronidase were added. It has been said that the rate of absorption under these circumstances approximates the rate after intravenous injection. While an increased absorption rate has been established for subcutaneous infusions, no controlled studies on the effect of hyaluronidase on the absorption of drugs after single, small-volume injections have yet been made.

The study reported was done as a class experiment in medical pharmacology. Phenol red was injected by different parenteral routes (intravenous, intramuscular, subcutaneous and subcutaneous with hyaluronidase) and the dye excretion was followed at half-hour intervals for 2 hours.

Methods. Sixty-seven medical students participated in the experiment. On the day of the study, no breakfast was taken, and half an hour prior to the phenol red injection each student drank 500 ml. of tap water. The students were divided into 4 experimental groups, one for each type of administration. The injections of dye alone were given from 1-ml. tuberculin syringes intravenously (antecubital vein), intramuscularly (deltoid) or subcutaneously (upper arm). The students who received phenol red + hyaluronidase were first tested for sensitivity by an intra-

*This investigation was supported in part by a research grant, RG–3795, from the National Institutes of Health, United States Public Health Service.

dermal injection of 0.02 ml. (10 viscosity units) hyaluronidase*. None revealed any signs of sensitivity. For the excretion experiment 1 ml. phenol red (6 mg.) and 1 ml. (500 viscosity units) of the hyaluronidase were injected simultaneously from a 2-ml. syringe. All injections were made under close supervision. Except for mild soreness and itching of short duration after the subcutaneous administration of the dye, no side effects were observed during the experiment.

Urine was collected at half-hour intervals, and after each collection, 250 ml. of tap water were taken. The determinations of phenol red in the urine were made according to Hawk, Oser and Summerson[8].

Results. The data and the statistical analysis are presented in Table 1. In Fig. 1 the cumulative per cent of dose excreted after administration by different routes is plotted against time. It was found that the dye was significantly more rapidly excreted after intravenous administration, while after intramuscular injection excretion was delayed. As can be seen from Fig. 1, the total amount excreted in 30 minutes after intravenous injection was only equalled 70 minutes after intramuscular injection. The 10-minute time allowance ordinarily used after intramuscular administration of the dye in performing kidney function tests is, therefore, too short and should be replaced by a 40-minute allowance if intramuscular injections are used.

Subcutaneous injections of phenol red, with or without hyaluronidase, were absorbed still more slowly, though the difference after one hour between the means for intramuscular and subcutaneous administration was not significant. A comparison of the two methods of subcutaneous administration revealed that the addition of hyaluronidase did not increase absorption significantly, though the curve was apparently closer to the intramuscular excretion curve than that of subcutaneous administration without hyaluronidase.

As can be seen from the coefficient of variation of the various experimental groups, the narrowest range of values was observed after intravenous administration. All other routes showed more scatter. The data also show that variability decreased with increasing time. A sharper definition of the "normal" excretion was obtained with longer collection periods. This was true for all the routes studied, but particularly so for intravenous administration.

Discussion. In 1905 Meltzer and Auer[14] were able to demonstrate that drugs are more rapidly absorbed after intramuscular than after subcutaneous administration, but Rowntree and Geraghty[21] provided definitive data. A dispute, dating back half a century, was brought to an end by their experiments which were made possible by a careful study of the pharmacological properties of phenol red. It was shown to be a harmless drug which could be administered by any route and which could be evaluated quantitatively by a simple analysis of the urine.

Rowntree and Geraghty[20] had begun their investigations into the use of phenol red as a kidney function test in 1910. They proposed to inject 6 mg. of the dye intravenously or intramuscularly and to measure the total excretion after 1 and 2 hours. Various modifications of this procedure have been suggested. Shaw[24] introduced the fractional urine collection at 15-minute intervals after intravenous administration of phenol red, a procedure used extensively today.

In spite of several drawbacks of theoretical as well as practical nature, phenol red excretion is probably the most extensively used test for the evaluation of kidney function. Although

*Hyaluronidase (Alidase) was generously supplied by G. D. Searle & Company, Chicago, Illinois.

TABLE 1.—THE URINARY EXCRETION OF PHENOL RED FOLLOWING PARENTERAL ADMINISTRATION BY VARIOUS ROUTES

Route of Administration	*Intravenous*				*Intramuscular*				*Subcutaneous*				*Subcutaneous with Hyaluronidase*			
Elapsed time in minutes	30	60	90	120	30	60	90	120	30	60	90	120	30	60	90	120
No. observations	18	18	18	18	16	16	16	16	18	18	18	18	15	15	15	15
Mean mg. excreted	3.56	4.56	5.09	5.32	1.65	3.21	4.13	4.65	1.10	2.31	3.18	3.79	1.22	2.51	3.62	4.27
Per cent dose excreted	59.3	76.0	84.8	88.7	27.5	53.5	68.8	77.5	18.3	38.5	53.0	63.2	20.3	41.8	60.3	71.2
Standard deviation mg.	0.95	0.57	0.44	0.38	0.73	0.90	0.87	0.76	0.44	0.61	0.74	0.76	0.45	0.68	0.84	0.72
Coefficient of variation	27%	13%	9%	7%	44%	28%	21%	16%	40%	26%	23%	20%	37%	27%	23%	17%
Significance of Results—P-values	I.V.				<0.001	<0.001	<0.001	<0.02	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
	I.M.				...	...	...	...	<0.02	<0.01	<0.01	<0.01	<0.05	<0.05	<0.02	<0.02
	S.C.				...	...	...	...	...	...	...	...	<0.3	<0.4	<0.2	<0.2

intravenous administration of the dye is believed to give more reliable results, there are still many texts which suggest the intramuscular route. From our experiments and those of Fromme and Rubner[5] it is obvious that there is a marked difference between the rates of excretion following intramuscular and intravenous administration. Our data also show that this difference, especially for the one-half and one-hour collections, cannot be corrected by an extra time allowance of 10 minutes for the intramuscular injection. Consequently, the indiscriminate use of the intravenous or intramuscular routes may lead to confusion and result in an erroneous definition of the "normal."

Mitchell, Owens and Valk[15] have recently shown a somewhat better correlation between PAH-clearance and phenol red excretion if the total excretion after one hour is used instead of the first 15 minutes. Without entering into the much disputed problem of which time interval should be used for the evaluation of kidney function, it should be pointed out that after intravenous administration the variability of the values in healthy individuals is less after the longer time.

The first studies on the excretion of phenol red after administration by different routes were done by Rowntree and Geraghty[21]. After preliminary experiments in animals, they followed the excretion in a few men and observed the following total excretion in per cent of the administered dose after one hour: intravenous 68, intralumbar 54, intragluteal 51 and subcutaneous 47%. These may be compared with our one-hour excretion data (Table 1) which were 76, 54 and 39% for the intravenous, intramuscular and subcutaneous routes, respectively. Since then phenol red has been used repeatedly in absorption studies. Abramson *et al.*[2] employed it as an indicator for the absorption of inhaled mists. Gardner and Nosik[6] in-

vestigated its excretion after injection into the subarachnoid space, but wide variability, even in healthy individuals, prevented its use as a tool for the measurement of cerebrospinal fluid absorption. Seifter, Baeder and Begany[23] studied phenol red excretion following intra-articular injection in rabbits to

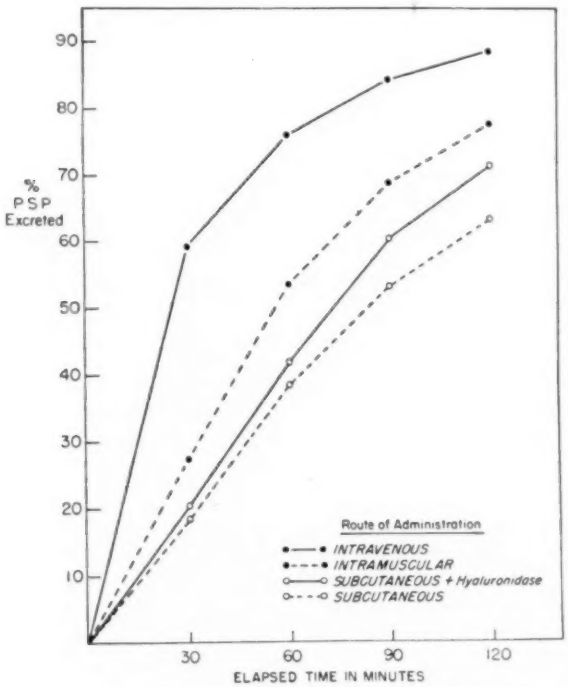


Fig. 1.—Cumulative per cent excretion of injected phenol red.

evaluate the effects of hyaluronidase and adrenal steroids on synovial permeability.

After subcutaneous administration of phenol red, the recovery is less than after intravenous injection, and after oral administration, it is still less. Abel and Rowntree[1] observed that phenol red was excreted in the bile regardless of the route of administration, but it was more completely reabsorbed from the intestine than other phthalein compounds. Penner, Hollander and Saltzman[19] demonstrated that the drug was not absorbed from the stomach. Möller and Lundsgaard[16] recovered less than 8% from the urine and usually less than 5% from the feces after administering it *per os*, and their *in vitro* studies showed that it was destroyed by feces but not by stomach contents. Similarly Hanner and Whipple[7] found that 3 to 5% of an oral dose appeared in the urine with only traces in the feces. They also observed that, following intravenous administration in the dog, 10 to 15% of the dye was excreted in the bile and approximately 85 to 90% in the urine. Macht[12] made the interesting observation that excretion was delayed by saline purgatives after oral or parenteral administration of phenol red.

These facts suggest a cycle of biliary excretion and intestinal reabsorption with a small fraction becoming trapped in the feces and destroyed. When intravenous injection is used, this intestinal loss is relatively unimportant; however, when absorption is delayed, intestinal loss is likely to be greater and recovery from urine less.

A second mechanism leading to poorer recoveries with slow absorption was suggested by the work of Kendall[11] which demonstrated that phenol red was metabolized anaerobically by many tissues, particularly by the liver. In a different way this was demonstrated by Major[13] who found depressed and irregular excretion after intrahepatic injection of phenol red in the rabbit.

During the last 30 years the renal excretion of the drug has been studied extensively, and an exhaustive review is given by Smith[26]. It need only be mentioned that the dye is excreted in part by filtration but chiefly by tubular secretion.

Hyaluronidase has been used extensively to increase the rate of absorption of local anesthetics and subcutaneous infusions. Forbes' *et al.*[4] investigations with small volume injections of radioactive Na^{24} have shown that it increases the absorption rate. Similarly the intravenous or intramuscular administration of penicillin, Moseley and Montgomery[17], streptomycin, Schwartzman, Henderson and King[22], heparin, Tuchman and Moolten[27] and other drugs has been replaced by subcutaneous administration with hyaluronidase. In very few of these studies have comparative assays of different methods of drug administration been made. A number of authors have claimed excellent results using hyaluronidase to accelerate the absorption of contrast media from subcutaneous sites, Simon and Narins[25], for use in pyelography, Burket and György[3], Hinman[10] and Olssen and Löfgren[18]. The only comparative study on the effect of hyaluronidase on the subcutaneous injection of phenol red was done by Burket and György[3]. They were not able to demonstrate increased absorption from the subcutaneous site following previous injection of hyaluronidase. Our own experiment confirms that phenol red is not absorbed significantly more rapidly or completely from the subcutaneous tissue if given with hyaluronidase.

Several factors might explain this difference in the effect of hyaluronidase on subcutaneous infusions or injections. It has been stated by Hechter, Dopkeen and Yudell[9] that the effect of the enzyme on absorption is proportional to its diffusion which, in turn, is primarily determined by the volume infused and the pressure applied. In subcutaneous injections of phenol red both pressure and volume are minimal; therefore, enzyme diffusion and pressure are slight and the increase in absorption may be negligible. We know of no explanation for the difference in behavior of phenol red and the Na^{24} used by Forbes. The good results which were observed after subcutaneous administration of contrast media with hyaluronidase were all reported in children, and it is well known that hyaluronidase has a much more profound effect on "young" connective tissue.

Though very few side effects have been observed after hyaluronidase, it is clear that an increase in the absorption rate in adults after single, small-volume injections of drugs is not the rule. More comparative studies should be done before such a procedure is used routinely for the replacement of intravenous or intramuscular administration of drugs.

Summary. Subcutaneous administration of phenol red with or without added hyaluronidase has been com-

pared with intravenous and intramuscular injections by studying the urinary excretion of the dye of 67 medical students. The delay in excretion following intramuscular administration was 40 minutes greater than after intravenous, and that following subcutaneous injection was still longer. Addition of hyaluronidase to the subcutaneous injection did not significantly increase the rate or completeness of absorption.

REFERENCES

1. **Abel, J. J.**, and **Rowntree, L. G.**: J. Pharmacol. & Exper. Therap., **1**, 231, 1909–1910.
2. **Abramson, H. A., Reiter, C., Gettner, H. H.**, and **Sklarofsky, B.**: Ann. Allergy, **7**, 761, 1949.
3. **Burket, L. C.**, and **György, P.**: Pediatrics, **3**, 56, 1949.
4. **Forbes, G. B., Deisher, R. W., Perley, A. M.**, and **Hartman, A. F.**: Science, **111**, 177, 1950.
5. **Fromme, F.**, and **Rubner, C.**: Berl. klin. Wchnschr., **49**, 1889, 1912.
6. **Gardner, J. W.**, and **Nosik, W. A.**: A.M.A. Arch. Neurol. & Psychiat., **41**, 484, 1939.
7. **Hanner, J. P.**, and **Whipple, G. H.**: A.M.A. Arch. Int. Med., **48**, 598, 1931.
8. **Hawk, P. B., Oser, B. L.**, and **Summerson, W. H.**: Practical Physiological Chemistry. 13th ed. New York and Toronto: Blakiston Co., 1954, pp. 966–967.
9. **Hechter, O., Dopkeen, S. K.**, and **Yudell, M. H.**: J. Pediat., **30**, 645, 1947.
10. **Hinman, F.**: A.M.A. Arch. Surg., **63**, 585, 1951.
11. **Kendall, E. C.**: J. Am. Med. Assn., **68**, 343, 1917.
12. **Macht, D. L.**: J. Urol., **7**, 271, 1922.
13. **Major, R. H.**: J. Am. Med. Assn., **81**, 1362, 1923.
14. **Meltzer, S. J.**, and **Auer, J.**: J. Exper. Med., **7**, 59, 1905.
15. **Mitchell, A. D., Owens, R.**, and **Valk, W. L.**: J. Urol., **71**, 230, 1954.
16. **Möller, E.**, and **Lundsgaard, C.**: Acta med. Scandinav., **63**, 277, 1925–1926.
17. **Moseley, V.**, and **Montgomery, B. M.**: J. South Carolina Med. Assn., **46**, 244, 1950.
18. **Olssen, O.**, and **Löfgren, O.**: Acta radiol., **31**, 250, 1949.
19. **Penner, A., Hollander, F.**, and **Saltzman, M.**: Am. J. Digest. Dis., **5**, 657, 1938–1939.
20. **Rowntree, L. G.**, and **Geraghty, J. T.**: J. Pharmacol. & Exper. Therap., **1**, 579, 1909–1910.
21. Iidem: A.M.A. Arch. Int. Med., **9**, 284, 1912.
22. **Schwartzman, J., Henderson, A. T.**, and **King, W. E.**: J. Pediat., **33**, 267, 1948.
23. **Seifter, J., Baeder, D. H.**, and **Begany, A. J.**: Proc. Soc. Exper. Biol & Med., **72**, 277, 1949.
24. **Shaw, E. C.**: J. Urol., **13**, 575, 1925.
25. **Simon, N.**, and **Narins, L.**: Am. J. Roentgenol., **61**, 91, 1949.
26. **Smith, H. W.**: The Kidney. New York: Oxford University Press, 1951, pp. 171–182.
27. **Tuchman, M. S.**, and **Moolten, S. E.**: Am. J. Med. Sci., **219**, 147, 1950.

SUMMARIO IN INTERLINGUA

Le Effecto de Hyaluronidase Super le Absorption de Rubio Phenolic in Administrationes Subcutanee

Administrationes subcutanee de rubio phenolic—sin o con addition de hyaluronidase—esseva comparate con administrationes intravenose e intramuscular per studiar le excretion urinari del colorante in 67 studentes medical. Le retardo del excretion post administrationes intramuscular esseva 40 minutas plus longe que post administrationes intravenose. Post administrationes subcutanee, le retardo esseva ancora plus longe. Le addition de hyaluronidase al dose de administration subcutanee non augmentava significativemente le volumine o le grado del absorption.

MALARIA IN VETERANS OF THE KOREAN WAR: A REVIEW OF 128 ADMISSIONS FOR MALARIA TO A VETERANS HOSPITAL*

By Robert Schwartz, M.D.
FORMERLY CHIEF, MEDICAL SERVICE, VETERANS ADMINISTRATION HOSPITAL AND CLINICAL ASSOCIATE PROFESSOR OF MEDICINE, UNIVERSITY OF PITTSBURGH SCHOOL OF MEDICINE

AND

William B. Tuttle, M.D.
FORMERLY RESIDENT, INTERNAL MEDICINE, VETERANS ADMINISTRATION HOSPITAL ASPINWALL, PENNSYLVANIA

(From the Medical Service, Veterans Administration Hospital, Aspinwall, Pennsylvania, and the University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania)

Experience in hospitals of the Veterans Administration indicates a parallelism between the number of patients discharged from the military service and the number of cases of malaria admitted to the hospital (See Figs. 1 and 2). This observation at the Veterans Administration Hospital, Aspinwall, Pa., in World War II veterans was reviewed in a previous article[1]. The present report deals with observations on the occurrence and clinical characteristics of malaria in veterans of the Korean War and the effect of the introduction of the newer antimalarial agents in suppression and treatment of the disease.

During the years 1951 to 1954 inclusive, 128 cases of malaria were encountered at this institution. One hundred and seventeen veterans of the Korean War were responsible for 126 admissions for malaria. Nine patients had a second admission for recurrent malaria following treatment at this hospital. Two cases were excluded from this study. One was a female veteran who had served only in the continental United States and who developed malaria following a blood transfusion. The other was a World War II veteran who had experienced five recurrences of malaria following an initial episode in 1945.

There was a progressive rise in the number of personnel discharged from the Armed Forces, from 43,665 in 1951, to 637,027 in the first six months of 1953 (See Fig. 3). The number of patients with malaria admitted to Aspinwall Veterans Administration Hospital rose from 3 in March, 1951, to a peak of 20 in August, 1952 (See Fig. 4). Thereafter, the number of admissions for malaria decreased abruptly. This change perhaps can be ascribed to the initiation in August, 1952, of the mass primaquine treatment of military personnel leaving Korea.

Clinical findings. The majority of the patients gave a history of having received suppressive antimalarial therapy while in Korea. Only 5 men denied

*Sponsored by the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are a result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

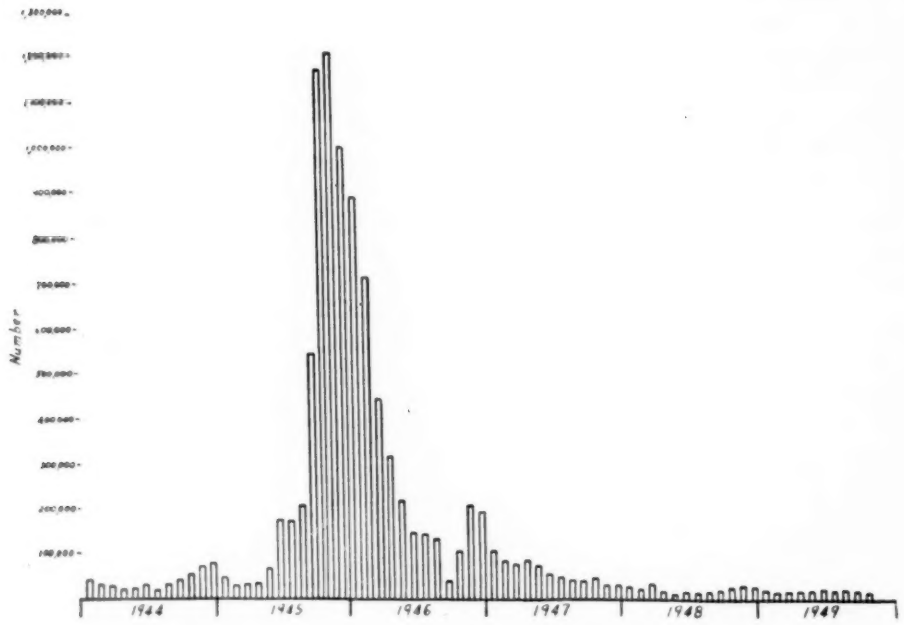


Fig. 1.*—Monthly discharges of Army and Air Force personnel in the United States from January, 1944, to December, 1949 (Courtesy of the Adjutant General, Department of the Army).

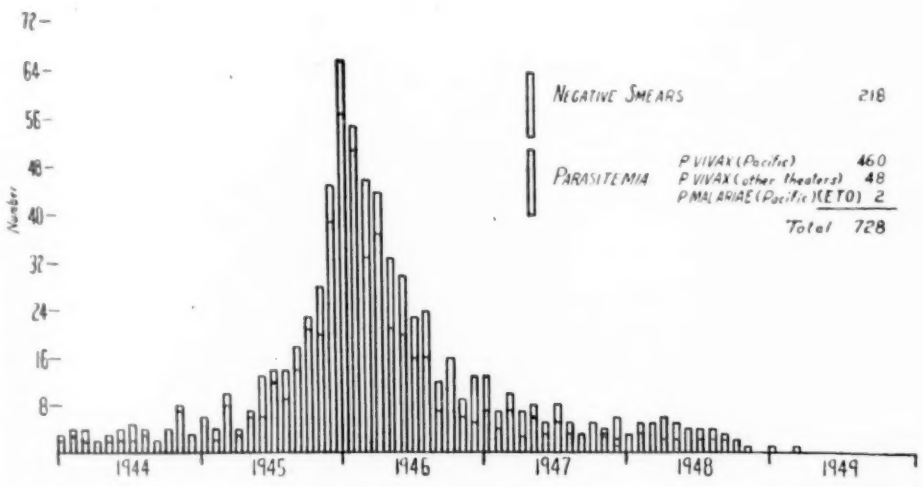


Fig. 2.*—Monthly admission to Aspinwall, Pa., Veterans Administration Hospital from January, 1944, to December, 1949.

*Figs. 1 and 2. Permission for reproduction has been granted by the Archives of Internal Medicine. These charts appeared originally in Archives of Internal Medicine—Schwartz, Mansuy, and John, December, 1950.

receiving such medication. Only 15 of the 117 patients reported having received routine primaquine therapy during their return to the United States. These cases are assumed to represent failure of the curative action of primaquine. Twenty-nine patients stated that they had been treated for malaria while in the war zone or following their return to the United States.

The interval between the time of leaving Korea until hospitalization for malaria varied from one to 15 months and averaged 6.7 months.

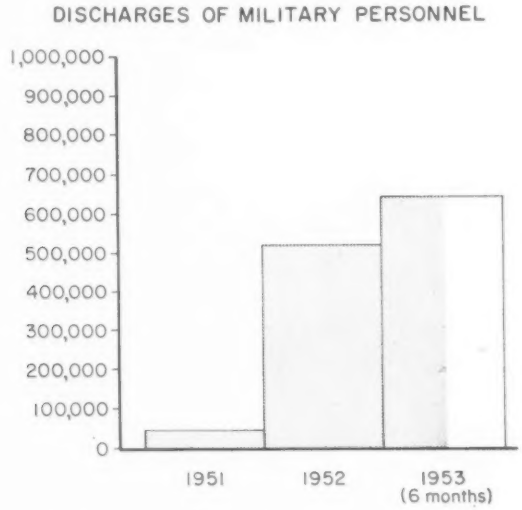


Fig. 3.—Discharges of military personnel from 1951 through the first six months of 1953.

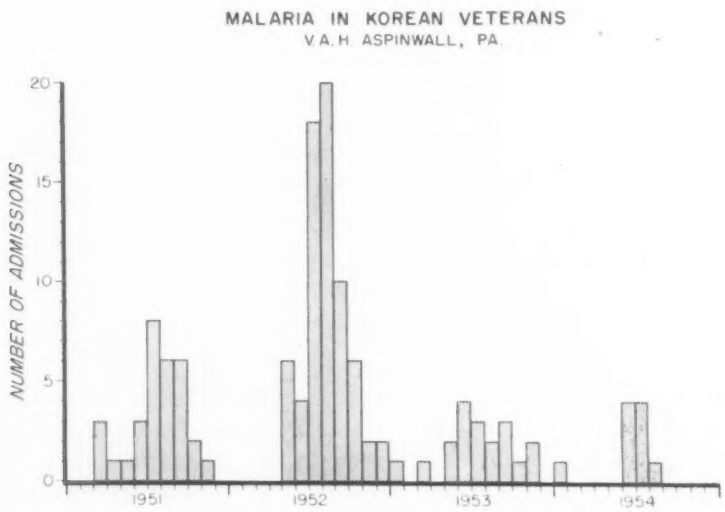


Fig. 4.—Monthly admissions to Aspinwall, Pa., Veterans Administration Hospital from January, 1951, to December, 1954.

Chills, fever, muscle aching, anorexia, nausea, and vomiting were the most common symptoms. Fever was present in every case; the highest oral temperature recorded in any case was 106° F. Jaundice was apparent in 2 cases. In 80 patients (63%), the spleen was palpable and in 6 patients (5%) the liver was palpable. Herpes simplex was present in 17 patients (13%).

LABORATORY FINDINGS. *Plasmodium vivax* was demonstrated in the blood of every patient. In one case *Plasmodium malariae* was found in addition to *Plasmodium vivax*.

Anemia (red blood cell count below 4,200,000 per c.mm.) was present in 53 cases (42%). The most severe anemia was found in a patient whose red-cell count was 1,920,000 and who had a marked leukemoid reaction. The degree of anemia was usually directly related to the duration of the symptoms prior to hospitalization. Relative leukopenia was observed in most cases. White blood counts ranged from 3,000 to 12,600 per c.mm., with 32% of the patients having counts below 6,000 per c.mm.

Proteinuria of slight degree was noted in 14 cases.

In 4 cases serologic tests for syphilis were positive. Clinical evidence of syphilis was present in only one of these patients.

Miscellaneous findings included abnormal cephalin flocculation and thymol turbidity tests in 4 patients, and the presence of *E. histolytica* in the stools of 3 patients.

Results of Treatment. Treatment of all cases consisted of the administration of 2.5 gm. of chloroquine phosphate in divided doses over a period of 72 hours. In every instance there was prompt clinical improvement with disappearance of malaria parasites from the blood. All patients admitted after June, 1953, received 15 mg. of primaquine base daily for 14 days subsequent to the course of chloroquine. There were no readmissions for malaria in the patients who received primaquine at this institution.

Summary. During the years 1951 to 1954 inclusive there were 126 veterans of the Korean War admitted for malaria at the Aspinwall Veterans Administration Hospital.

A significant reduction in the number of admissions for malaria was observed following the institution of mass primaquine therapy of military personnel in August, 1952. Fifteen patients who apparently had received primaquine during their return to the United States subsequently developed clinical manifestations of malaria.

Malaria developing in veterans of the Korean War, as compared with the disease as it was observed in veterans of World War II, was characterized by a longer latent period, higher incidence of splenomegaly, and a lower incidence of false positive serologic tests for syphilis. Chloroquine proved to be effective in relieving symptoms.

REFERENCE

1. **Schwartz, R., Mansuy, M. M.,** and **John, W. C.:** A.M.A. Arch. Int. Med., **86,** 837, 1950.

(Interlingua on page 600)

PROGRESS
OF
MEDICAL SCIENCE

RADIOLOGY

UNDER THE CHARGE OF

DAVID M. GOULD, M.D.
PROFESSOR OF RADIOLOGY
UNIVERSITY OF ARKANSAS MEDICAL CENTER
LITTLE ROCK, ARKANSAS

AND

JOHN G. MCAFEE, M.D.
ASSISTANT PROFESSOR OF RADIOLOGY
THE JOHNS HOPKINS UNIVERSITY AND HOSPITAL
BALTIMORE, MARYLAND

RADIOLOGICAL DIAGNOSIS OF DISEASES OF ADRENAL ORIGIN

BY JOHN G. MCAFEE, M.D.
ASSISTANT PROFESSOR OF RADIOLOGY

AND

CARL E. BALLI, M.D.
ASSISTANT RESIDENT IN RADIOLOGY

(From the Department of Radiology, The Johns Hopkins University and Hospital, Baltimore, Maryland)

RAPID advances in the clinical and biochemical aspects of adrenal diseases have caused renewed interest in the radiological features as well. A simple practical method for the radiographic delineation of the adrenal gland itself was not available until the development of pre-sacral gas insufflation in 1947[161,162]. Since then, many papers have been written on the radiological findings in the various types of adrenal disease.

The pertinent literature on this subject is reviewed from 1940 onward. The available methods for the radiological demonstration of the adrenal glands are reviewed, and the abnormal radiological findings which have been described in each type of adrenal disease are summarized. It will be apparent that there remain many gaps in our knowledge of this sphere of diagnostic radiology.

Diagnosis of Adrenal Tumors by Conventional Radiological Techniques. On plain films of the abdomen, it is possible in a few patients to visualize the outline of the normal adrenal glands, because of the presence of surrounding fatty tissue[166]. An adrenal tumor, if

large enough, may be demonstrated as a soft tissue mass, and calcifications may be demonstrated, on occasion, in almost any type of adrenal tumor.

Intravenous or retrograde pyelography enhances the demonstration of adrenal tumors considerably. In one series of 39 tumors proven by surgery[94], 74% were demonstrated by pyelography.

Fig. 1.—Virilizing right adrenal cortical adenoma shown on intravenous urogram. The globular tumor mass is seen depressing and rotating the right kidney.

There is usually depression of the kidney on the affected side, often accompanied by anterior displacement on lateral films[61,166]. Some degree of renal rotation is frequently present, with the upper pole lying medial to the lower pole (Fig. 1); this is the reverse of that usually seen in renal ptosis[21]. Larger tumors may depress and deform the upper renal calyces and may be difficult or impossible to differentiate from renal tumors of the upper pole[21]. In erect pyelogram films, however, the mobile kidney may fall away from the fixed adrenal tumor[87]. Laminography of the adrenal areas may be used alone or in conjunction with pyelography; frequently, however, confusing soft tissue shadows render accurate interpretation impossible.

In gastrointestinal series, left adrenal tumors have been detected by forward, medial, or upward displacement of the barium-filled stomach[61,104]. Right adrenal tumors have been demonstrated by anterior displacement of the descending portion of the duodenum as seen in right lateral films[61,121]. In barium enemas, adrenal masses may cause depression of the flexure of the colon on the side of the tumor[4].

Pre-sacral Gas Insufflation (Retroperitoneal Pneumography: Pneumoretroperitoneum). The adrenal glands may be visualized fairly well by pneu-

moperitoneum[166], but gas insufflation of the retroperitoneum is much superior. Carelli first developed the technique of perirenal gas insufflation using carbon dioxide through a translumbar puncture in 1920, and published his technique in 1921[26,27]. Cahill[18] demonstrated a variety of adrenal lesions with this method. However, it failed to gain popularity. In 1947, Ruiz Rivas[161,162] first developed the pre-sacral method of gas injection, and this quickly came into widespread use. This procedure has remained the simplest and best method of demonstrating the adrenal glands[190]. It has the following advantages over the perirenal injection: (1) the renal and adrenal areas of both sides can be outlined from a single needle puncture; in the perirenal method, each side must be punctured. (2) It is safer, because the danger of gas embolism is somewhat less[40]. The retrorectal tissues, into which the needle is inserted in the pre-sacral method are relatively avascular[162]. The hazards of gas embolism using the perirenal method are especially great in vascular thin-walled tumors[20]. (3) It is technically easier to perform[17,40]. In the translumbar method, the insertion of the needle must be precise anatomically[100]. If the needle penetrates too deeply, into the kidney, pain is produced. Correct insertion of the needle is more difficult in obese patients[100]. Variations in the anatomical position of the kidney render the perirenal insertion more difficult, but are of no consequence in pre-sacral studies. (4) The retroperitoneal planes of the psoas muscles are well outlined by the pre-sacral route and para-aortic tumors may be demonstrated[17]. (5) The danger of pneumothorax[159] is completely avoided by the pre-sacral method.

TECHNIQUE. The knee-chest position[16,93,152,174] may be used, but is not very satisfactory because the patient is apt to move during the procedure. The Blackwood position[12] is often used, with the patient lying in the lateral decubitus position with the spine flexed and the knees drawn up under the chin. This is quite satisfactory when only one side of the body is to be examined, but unfortunately, in order to fill the dependent side with gas, it is necessary to turn the patient into the other lateral decubitus position with the needle in place. The prone position is most satisfactory from the standpoint of both the operator and the patient[178]. Lying crosswise on the radiological table, both thighs extending over the side and with a pillow under the abdomen, the patient is fairly comfortable, cannot move, and both sides are filled simultaneously.

After the patient has been sedated and positioned, the index finger of the gloved left hand is inserted into the rectum. Topical anesthetic ointment may be used on the index finger to minimize anal discomfort[179]. Following local procaine infiltration, a number 18 or 20 three-inch lumbar-puncture needle[12,16,64,154] is inserted at the midline between the rectal finger and the tip of the coccyx[12] through the ano-coccygeal raphe[64] and into the retro-rectal space. The insertion of the finger into the rectum is necessary to avoid rectal perforation. Before injecting the gas, it is of prime importance to aspirate the needle with a syringe to guard against gas embolism; if blood is aspirated the needle should be immediately withdrawn, and the examination postponed[179]. The gas may be injected with a simple syringe and three-way stop-cock. Some authors have found a two-bottle pneumothorax apparatus[16,180] more convenient, using a hydrostatic pressure of 15 to 30 cm. of water. Regardless of the method of injection, the rate must be slow[49]. As few as 600 ml.[48] and as many as 2000 ml.[16] have been used in adults, but the usual volume is 1000 to 1200 ml.[49,64]. In infants 100 ml. may be used[49] and in children 400 to 600 ml.[56,64] (15 ml. per kilogram body weight[179]). Some authors advocate using an absorbent cotton filter in the system[152,179]. The gas may be injected through #50 fine polyethylene tubing which is inserted through the lumen of the needle[131]. After withdrawal of the needle, the patient is instructed to sit up and perform flexion movements of the trunk to diffuse the gas through the retroperitoneum[40,67].

Antero-posterior, postero-anterior, and both oblique films of the adrenal areas should be obtained[3]. If the adrenal shadows are not readily separated from the renal shadows, erect films should be taken[180]; in this position the adrenals remain fixed in position be-

cause they are firmly attached to the apex of Gerota's fascia, and the kidneys descend. Tomograms of the adrenal areas between 5 and 12 cm. depths are indispensable because of the frequency of confusing soft tissue shadows on plain films[3,124,192,199]. Sometimes adrenal lesions are best demonstrated on lateral tomograms[174]. If the initial films fail to show satisfactory delineation of the adrenal glands with the gas, films taken several hours later may be helpful. Many authors combine the procedure with pyelography[40,48].

A variety of gases have been used for the insufflation, including air, oxygen, helium, carbon dioxide, and nitrous oxide.

COMPLICATIONS. Several series of gas insufflations, each containing from 200 to 400 patients, have been done without fatality or serious complication[20,64,107,159]. Mosca collected a series of 1,500 examinations without fatal incidents[126]. Steinbach and Smith collected almost 2,000 studies from 17 institutions, including 350 of their own, without serious complications or deaths[180].

Minor complications from the procedure are well known. Rectal discomfort[179], transient lumbosacral discomfort, and a feeling of fullness in the epigastrium and groins as the gas diffuses upwards, are almost universal[12,40,152,159]. About half of the patients experience transient pain in the shoulders from diaphragmatic irritation[152]. When the needle tip is too superficial, subcutaneous emphysema develops in the perineum or scrotum[56,159,179], but this is simply corrected by deeper insertion. Occasionally, there is emphysema of the abdominal wall[40]. When excessive volumes of gas are used, subcutaneous emphysema of the neck appears; temporary hoarseness or loss of voice have been produced by involvement of the larynx[162]. Occasionally the rectum has been accidentally perforated, but this has apparently caused no serious complication[40,174].

Except for a few isolated case reports, the only serious complication from gas insufflation has been gas embolism. In one patient, bilateral ureteral obstruction and anuria developed following a pre-sacral study[48]. Renal hematoma has occurred from accidental puncture of the kidney during a perirenal insufflation[34]. One patient with a delayed clotting time developed serious retroperitoneal hemorrhage after a pre-sacral study[56].

When gas embolism occurs, syncope, dyspnea, cyanosis, shock, and sometimes a characteristic, loud "millwheel" cardiac murmur appear; gas may be detected in the cardiac chambers and great vessels radiologically. When these symptoms appear, the patient should be immediately placed in the left lateral decubitus position (left side down). Experimentally in dogs, large amounts of intravenous gas are tolerated in this position, because it tends to froth, becoming dispersed and absorbed in the lungs. In other positions, it is trapped in the outflow tract of the right ventricle causing obstruction of the pulmonary circulation[41]. The amount tolerated can also be increased by a slower rate of injection[41]. Several cases of recovery from gas embolism in man have occurred following placement in the left lateral decubitus position[130,163], but one death occurred in spite of this[180]. One fatality from gas embolism occurred from the relatively small injection of 15 ml. of air under spinal anesthesia during a perirenal insufflation[15]. Transient hemiplegia has been produced[180] by gas embolism.

An excellent clinical survey of the effects of gas embolism has been reported by Ransom[151]. In an analysis of 1,267 replies out of 1,736 questionnaires sent to the members of the American Board of Urology, a total of 58 deaths due to gas embolism were found. Thirty-four of these were from perirenal injections and 24 from pre-sacral injections. In addition, there were 64 severe non-fatal reactions of which 31

occurred in perirenal injections and 33 in pre-sacral injections. From this survey, it is apparent that gas insufflations are being done in increasing numbers since Ruiz Rivas introduced the pre-sacral technique. This method appears to be safer than the perirenal method. Irrespective of the technique involved, whether it was manometric or syringe, the safety of the procedure depended entirely on the gas used. Deaths occurred with air, oxygen, and helium, but none occurred with carbon dioxide or nitrous oxide, because of their high solubility in blood. Intravenous injection of carbon dioxide has been used even for angiocardiography in animals with safety (Stauffer, Durant and Oppenheimer[176a]).

Almost all deaths and serious complications from gas insufflation could be avoided if carbon dioxide were used, as originally described by Carelli[26,27]. Teschendorf[185] has used nitrous oxide and carbon dioxide satisfactorily in pneumothorax and pneumoperitoneum for over 30 years without complications.

CONTRAINDICATIONS. 1. Cases of neuroblastoma, because of the danger of dissemination of malignant tumor cells by the gaseous dissection of the retroperitoneal fascial planes[20,106].

2. Retroperitoneal or perirenal infections[56,100].

3. Peri-anal inflammations[154].

NORMAL ADRENAL VARIATIONS IN GAS STUDIES. Delineation of the adrenals with retroperitoneal gas is possible anatomically because the fascia of Gerota surrounding the kidney and adrenal forms a compartment which is closed laterally and cranially, but open medially and inferiorly[100]. Within the compartment lies the perirenal areolar fat through which gas may readily dissect.

The right gland is triangular and the left crescentic, but there are wide normal variations in both their size and shape[115]. The radiographic adrenal shadow is composed not only of the gland substance but also the surrounding fatty tissue and fascial ligaments[8]. The peri-adrenal fat may make the gland appear larger than it actually is, notably in Cushing's syndrome[180]. Oblique films and tomograms are essential for the accurate estimation of adrenal size, because frequently the glands extend behind the kidneys so that they are partially hidden on antero-posterior views. Steinbach and Smith[180] have established normal values for the area of the adrenal glands in antero-posterior films or tomograms as follows:

right adrenal—average 4.2 sq. cm. range 2.0 to 7.8 sq. cm.

left adrenal—average 4.3 sq. cm. range 2.0 to 8.7 sq. cm.

In some studies, the margins of the adrenals are vaguely demarcated. The border between the adrenal and kidney may be indistinct or absent[3,179,180]. The peri-adrenal fatty areolar tissue infiltrated with gas often creates a reticular or granular adrenal margin[3,192]. As gas dissects between the adrenal and kidney, the so-called "reticulated strands" of areolar tissue are especially prominent[180], producing a vertical streaking radiographically. The glands are better seen in thin people; visualization in obese subjects is more difficult and requires more gas[20]. In infants and children, the adrenals are relatively larger than in adults[20,49], especially in very young infants[183]; visualization in children is, therefore usually satisfactory[23,49].

The left suprarenal gland is often not as well demonstrated as the right because it is thinner[20] and more adherent to the left kidney[49]. Abdominal adhesions may prevent diffusion of the gas through the adrenal areas[154]. In some cases, it is not possible to diffuse gas around the adrenal even though no

abnormality exists[199]: diffusion may eventually occur, however, in delayed films[20]. The right adrenal is lower and often slightly more medial than the left[8]. Upward prolongations of the right gland extending along the adrenodiaphragmatic ligament are not unusual[8]. Downward extensions of the left gland along the medial border of planes, may render surgical dissections of the retroperitoneal tissues easier[174].

INTERPRETATION OF ABNORMAL ADRENAL SHADOWS. Roughly 70% of adrenal tumors and hyperplasias are diagnosed correctly by pre-sacral gas insufflations, as determined by subsequent surgery[3]. The small cortical nodules and adenomas which are frequently discovered

Fig. 2.—Bilateral adrenal hyperplasia on combined pre-sacral gas insufflation and intravenous urogram. Both glands are enlarged but their normal triangular shape is preserved. Postnatal adreno-genital syndrome.

the kidney may occur[179]. In 8% of gas studies, only one adrenal gland can be demonstrated[20]. Unilateral absence of the adrenal is not rare[25]; it occurs in about one-third of cases with unilateral renal agenesis.

Occasionally, gas may diffuse through the root of the mesentery surrounding the bowel, especially the cecum and sigmoid colon[174].

It has been suggested that gas insufflations, by separating out fascial incidentally at postmortem cannot be demonstrated in gas studies[20]. In adrenal hyperplasia, an increase in size of the gland is seen, but the normal triangular or crescentic shape is retained (Fig. 2). In tumors, on the other hand, the enlarging gland becomes globular[20,22,82,111,115,180]. Abnormal glands usually increase in density as well as in size[115]. In hormone-secreting tumors, the size of the mass bears no relation to its endocrine activity[148]. With these

tumors, atrophy of the opposite adrenal aids in the differentiation from diffuse hyperplasia, which is almost always bilateral[180]. The various histological types of adrenal tumor (as summarized in Table 1) are all radiologically indistinguishable, with the possible exception of neuroblastoma occurring in childhood.

TABLE 1.—CLASSIFICATION OF ADRENAL TUMORS

Modified after Karsner[95] and Cahill[20]

CYSTS:
- pseudo cysts (cystic degeneration of hematomas and adenomas)
- cystic lymphangioma
- true glandular cysts

CONNECTIVE TISSUE TUMORS:
- myoma, fibroma, neurofibroma, lipoma, "osteoma," hemanigoma, lymphangioma, hemangioblastoma, fibrosarcoma, myxosarcoma

TUMOR-LIKE LESIONS:
- hematoma
- cortical nodules
- myelolipoma (ectopic or metaplastic bone marrow)

CORTICAL TUMORS:
- adenoma (hormonal and non-hormonal)
- carcinoma (hormonal and non-hormonal)

MEDULLARY TUMORS:
- sympathicogonioma, sympathoblastoma } neuroblastoma
- ganglioneuroma
- pheochromocytoma (chromaffin cell tumor, paraganglioma)
- pheochromoblastoma (malignant pheochromocytoma)

SECONDARY TUMORS:
- direct extension from renal tumors
- metastatic carcinoma (breast, stomach, colon, lung, biliary tract and kidney, in descending order of frequency)
- lymphomas
- metastatic malignant melanoma

TERATOMA:

Radiographic "pseudo-tumors" of the adrenal areas have not been sufficiently appreciated as a cause of diagnostic error. The most notorious of these is the rounded density created by the fluid-filled gastric fundus[93] seen on supine antero-posterior abdominal films. This shadow may be eliminated by an erect or prone film of the abdomen, or may be converted into a radiolucent shadow by ingestion of a carbonated beverage[78,81] or an effervescent powder[124]. Similarly the fluid-filled pyloric antrum and duodenal bulb have simulated a right adrenal tumor, especially on prone abdominal films. Other "pseudo-tumors" which have created confusion even on gas insufflations, are: abnormal prominences of the tail of the pancreas[71,115], anomalous projections from the lobes of the liver[71,93], and lobulations of the spleen[82]. One large "pseudo-tumor" demonstrated on a gas study proved to be merely a large spherical mass of fatty tissue overlying a normal adrenal gland[180]. At The Johns Hopkins Hospital, isolated fetal lobula-

tion of the left upper renal pole has simulated the appearance of an adrenal tumor in two cases. Other retroperitoneal tumors[93] and hematomas of the adrenal gland[75,93,137] may look identical to adrenal tumors.

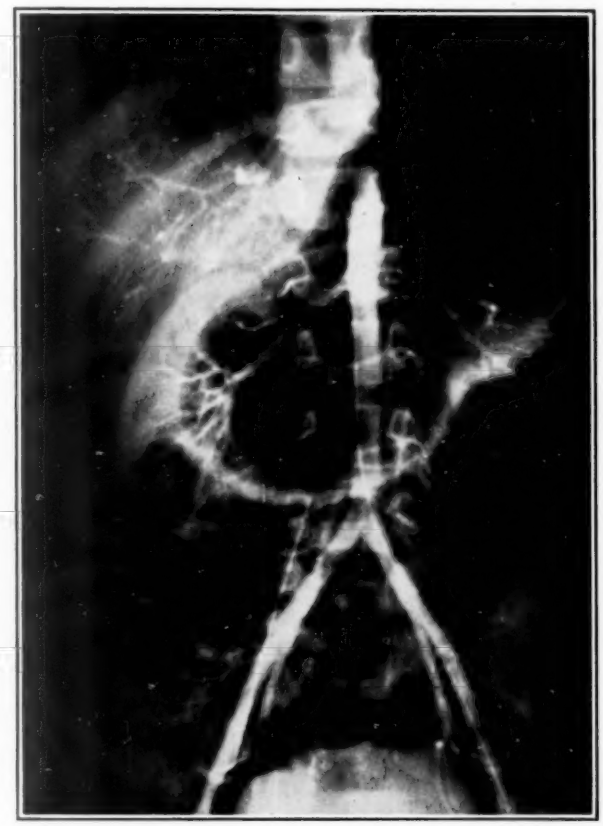


Fig. 3.—Masculinizing right adrenal cortical adenoma shown on abdominal aortogram. The adrenal vessels arising from the right renal artery and aorta are abnormally prominent. Diffuse "staining" of the contrast medium is seen in the adrenal area due to the increased vascularity of the tumor.

Abdominal Aortography. The technique and complications of this procedure have been recently reviewed in this journal[32]. The adrenal arteries are extremely small but nevertheless may be visualized by aortography. The normal arteries[25] consist of (1) a superior adrenal branch of the inferior phrenic artery or aorta, (2) an inferior adrenal branch of the renal artery or aorta, the vessel most often demonstrated by aortography, and (3) the middle adrenal branch, infrequently visualized. The adrenal arteries are frequently anomalous. The right vessels are often obscured by the hepatic artery or its branches[71] and the left vessels by the splenic artery.

Aortography has not been extensively used for the diagnosis of adrenal le-

sions. Several authors[48,71,77,96,193] have used the procedure in combination with retroperitoneal pneumography for adrenal lesions; the gas insufflation is usually performed on the same day prior to the aortogram. It has been possible to diagnose adrenal tumors on the basis of abnormal dilatation of the adrenal arteries and an abnormal "staining" in the area of the tumor due to an increase in number of fine adrenal vessels (Fig. 3). Thus, several pheochromocytomas[10,71,101,110,172] have been shown because of their increased vascularity; a few adreno-cortical tumors have also been diagnosed[71]. Small pheochromocytomas have been missed in aortograms[71]. One death due to aortography after visualization of a vascular pheochromocytoma has been reported[101]; shock was apparently precipitated by the injection of contrast medium and death occurred in 36 hours.

Neuroblastoma. This is the commonest and the most malignant adrenal tumor. The term "neuroblastoma" usually includes both the *sympathicogonioma* (neurogonioma)[202], a tumor of primitive sympathetic cells, very malignant, metastasizing readily and arising in embryonic life or infancy, and the *sympathicoblastoma* (sympathoblastoma)[191] arising from the sympathetic cells of intermediate maturation. "Neuroblastoma" does not usually include the benign *ganglioneuroma*. Over 100 cases of this benign tumor have been reported, chiefly in children[25], usually arising from the adrenal gland; many of these are calcified radiologically[63,206].

There is no sex predominance in neuroblastoma, and the tumor has been seen in all age groups from stillborn infancy[146] to late adulthood[50]. The average age of onset is about 4 years; approximately one-third occur in the first year of life and only 20% occur after the age of five[203]. Thirty-two cases were reported in newborn infants up to 1951[103]. The concept of Hutchinson's type[85] (left adrenal tumor metastasizing to skull, orbit, and neck) and Pepper's type[142] (right adrenal tumor in young infants metastasizing to the liver) is no longer held by most authors[29,143,188,205], because many transitional cases have occurred. Unusually, neuroblastoma may undergo spontaneous regression with hemorrhage and necrosis, or maturation into a benign ganglioneuroma[75,102,191,205].

ABDOMINAL FINDINGS. From 50%[168] to 75%[203] of these tumors have their site of origin in the abdomen. The remainder arise in the pelvis, mediastinum, neck, orbit, or skin[143,168,203]. In the abdomen, about 30% of the tumors arise from the adrenal glands, 50% from the lumbar sympathetic chains and in the remainder, the exact site of abdominal origin is indeterminate[58]. Abdominal neuroblastoma represents about 35% of all retroperitoneal tumors of childhood[173]. Early diagnosis and treatment when the disease is still confined to the abdomen is a most important factor in prognosis[153]; the outlook is particularly good if the disease is treated before it becomes symptomatic.

On plain films of the abdomen, an abnormal mass is demonstrated in 40% of all cases[168]. From 45%[168] to 57%[177] or roughly half of these[47,58,147] have calcifications within the mass (Fig. 4A). They are usually fine, multiple, and stippled but occasionally are large, irregular and confluent[117], or homogeneous, dense, and single[143]. Metastases in the retroperitoneal lymph nodes are the commonest site of spread[35,42] and these may be demonstrated as secondary soft tissue masses in antero-posterior and lateral views. Calcification in the retroperitoneal lymph node metastases as well as in the primary tumor may sometimes occur[135], and is characteristic of neuroblastoma. The liver is involved in

about one-third of the cases when first seen[203], either by metastases or by direct spread. It is usually best seen in the lateral films[168]. Metastases limited to this organ are common in young infants[75] and this involvement is not necessarily a bad prognostic sign[153]. Fluid in the abdomen is rare[117].

Abnormalities on pyelography occur in about 75% of cases with abdominal involvement[173,177]. Renal and ureteral displacement is usually seen[14] without intrinsic renal calyceal deformity[147]. The typical direction of renal displacement is downwards and outwards. The kidney may be rotated so that the upper pole is lying lateral to the lower pole[168]. It is often compressed but is rarely infiltrated[42]. Occasionally, anterior displacement is revealed on lateral films[118] in the absence of displacement on antero-posterior films. Hydronephrosis from pelvic or ureteral compression is often produced, both by the primary tumor and the retroperitoneal metastases. In unusual cases where the primary site of origin is in the pelvis, the tumor may distort the bladder contour in the pyelogram.

Gastrointestinal series have frequently revealed displacement of the stomach or small bowel especially on lateral films[14]. Lateral barium enema films may show anterior displacement of the flexures and transverse colon[118].

DIFFERENTIAL DIAGNOSIS FROM OTHER ABDOMINAL TUMORS IN CHILDHOOD. Neuroblastoma must be differentiated from the other common retroperitoneal tumors: Wilms's tumor and teratoma, and from the rarer lymphomas and rhabdomyosarcoma. Non-neoplastic masses such as hydronephrosis with renal enlargement[106], mesenteric cysts[205], and adrenal hematomas must also be considered.

Teratomas are neither as common nor as malignant as neuroblastoma and occur in infancy. On urograms, the tumor mass is usually near the midline displacing the kidneys laterally and sometimes contains fragments of bone or teeth[58].

Wilms's tumor (renal embryoma) is usually considered to be somewhat more common than neuroblastoma[75,173], but in a few series, neuroblastoma has been more common[117,205]. This tumor is intrarenal and well encapsulated; distortion and displacement of the renal calyces is almost invariable on urograms. When neuroblastoma distorts the renal calyces, it often becomes indistinguishable from Wilms's tumor[25,75]. This is especially true in the rare cases where neuroblastoma involves the renal parenchyma[80]. Wilms's tumor produces non-function of the involved kidney in one-third of the cases on intravenous pyelography[58], an uncommon finding in neuroblastoma[20]. It tends to metastasize to the lung parenchyma and pleura and rarely to the skeleton, whereas neuroblastoma commonly involves the skeleton and mediastinum, and rarely the lung parenchyma[58]. Calcification is seen in about 50% of neuroblastomas[168] but in only 8%[58] to 12%[177] of Wilms's tumors. Furthermore, the calcification is usually peripheral and linear or ring-like[17] in Wilms's tumor. The incidence of hematuria, hypertension, and fever due to tumor necrosis is somewhat higher in Wilms's tumor than neuroblastoma. Typically Wilms's tumor displaces renal structures downwards and medially and neuroblastoma, downwards and laterally[177].

LESIONS OF THE LONG BONES. Skeletal metastases are present in 40%[172,203] to 75%[168] of patients with this disease when first seen. Bone pain in the extremities or limp are presenting complaints in over one-third of the patients[153], and these are usually due to skeletal metastases. Because of this high incidence, the investigation of any patient with neuroblastoma is not com-

Fig. 4

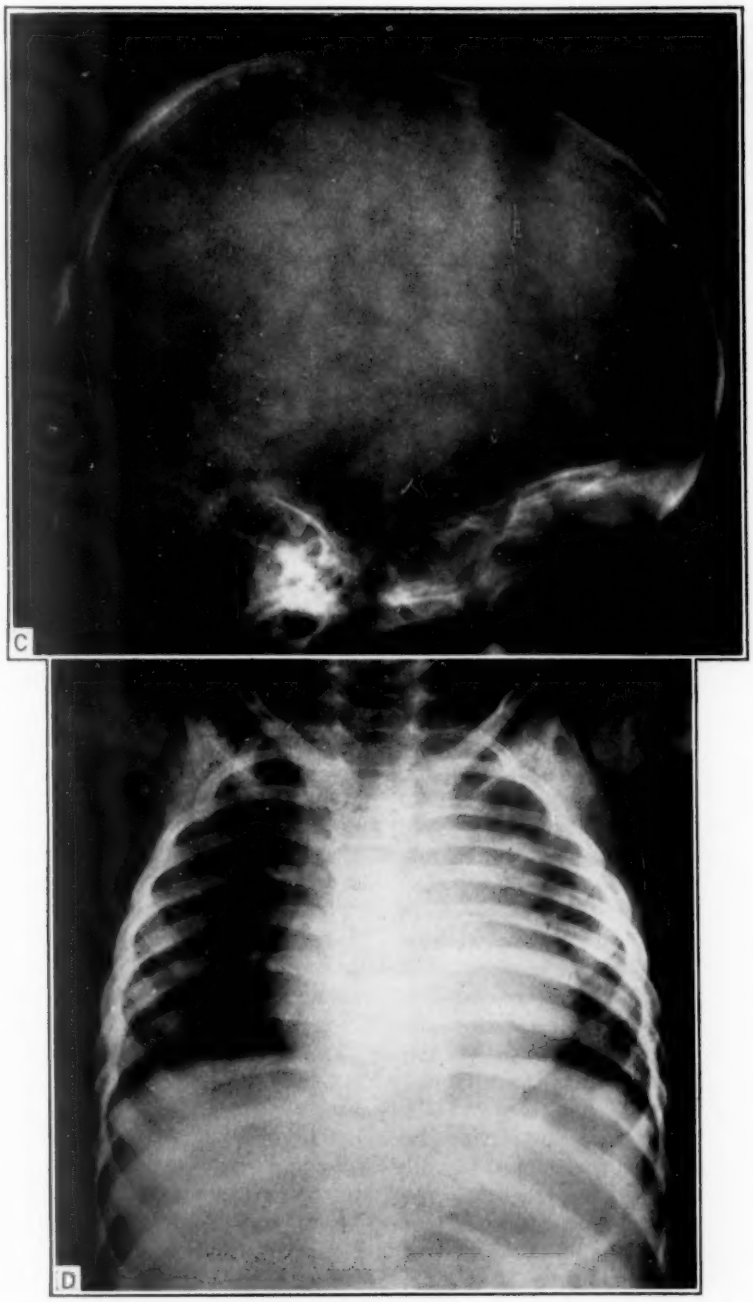


Fig. 4.—Neuroblastoma in childhood. *A*. Intravenous urogram reveals calcified mass in the right upper quadrant depressing the right kidney and obliterating its superior calyces and upper pelvis. The mild left hydronephrosis is due to tumor extension across the midline. *B*. Skeletal metastases in lower pelvis and femora. Multiple small areas of destruction are seen especially in the necks of the femora and ischii. Periosteal reaction is visible along the femoral shafts. Note the symmetrical distribution. *C*. Skull involvement. The spreading of the sutures due to increased intracranial pressure is accentuated by destructive changes at the suture edges. Minute foci of erosions are also seen in the parietal bones. *D*. Chest film shows a large metastasis in the left upper mediastinum, and small areas of destruction in the upper humeri and scapulae.

plete without a radiological survey of the entire skeleton[205]. Bone involvement, as a rule, indicates a bad prognosis[153], but a few isolated case reports of apparent cures have been encountered[5,79,191].

Lesions in the long bones are characteristically bilateral and symmetrical. Multiple fine destructive lesions are the commonest finding[84], usually beginning in the spongiosa, but often eroding the cortex (Fig. 4*B*). The changes may develop quite rapidly[168] and following radiologic therapy there is occasionally rapid improvement. The areas of erosion are often seen in the metaphyses[42] and along the medial borders of the shafts. Favorite sites are the medial aspect of the distal femoral metaphyses and the proximal humeral metaphyses[38,168]. The epiphyses are not frequently eroded[205]; they may rarely be involved alone. Sometimes the disease extends the entire length of a long bone[29,168]. The individual destructive lesions are occasionally quite large, and rarely may be isolated. Pathological fractures, though not common[84], may be seen in the femora or spine. Localized osteoporosis in the metaphyses of the long bones has been observed before actual destruction has appeared[38].

Periosteal reaction is seen in 60% of cases with bony involvement[168]. Sometimes it appears before destruction is evident[205] and sometimes its margin is quite irregular[29]. Radiating spicules or "sunburst" appearance extending beyond the bony cortex, as classically described in osteogenic sarcoma, has been seen occasionally in neuroblastoma as well as in a variety of other malignant neoplasms[76].

In a minority of patients, a soft tissue mass can be seen extending outwards from the bony surface, usually in an area of bony erosion.

The occurrence of transverse bands of decreased density at the metaphyses as seen in leukemia has been denied in neuroblastoma by Sherman and Leaming[168], but these have been seen in several patients with neuroblastoma at The Johns Hopkins Hospital.

DIFFERENTIAL DIAGNOSIS OF LONG BONE LESIONS. 1) Ewing's tumor of bone. 2) Leukemia. 3) Lymphosarcoma. 4) Osteomyelitis. 5) Congenital lues. 6) Schüller-Christian disease.

Both radiologically and pathologically the bone lesions in neuroblastoma may perfectly simulate the appearance of Ewing's tumor[1,7]. Both may cause destruction of the calvarium or osteolytic lesions in the shafts of the long bones with laminated periosteal reactions[7]. Ewing's tumor and neuroblastoma are often considered as variations in the same disease process[7]. In all cases of Ewing's tumor, therefore, a careful search for a retroperitoneal mass must be made[1].

The bone lesions of leukemia may be identical with those of neuroblastoma. Destructive lesions in the metacarpals and metatarsals, however, may occur in leukemia but not in neuroblastoma[58,205]. Evidence of bone production is never seen in leukemia but may occasionally be present in neuroblastoma[168]. General rarefaction of bone is sometimes seen in leukemia. Skull involvement is much less common than in neuroblastoma and soft tissue masses adjacent to bone are rarely seen[168].

The bone lesions due to the lymphosarcoma may be identical with those of neuroblastoma. However, they are often asymmetrical, accompanied by less periosteal reaction and less soft tissue mass formation[168].

SKULL LESIONS. The commonest finding in the skull is spreading of the cranial sutures due to increased intracranial pressure, from underlying metastases of the brain and meninges[29]. Sometimes only the coronal suture is

spread. Increased convolutional impressions of the inner table due to increased pressure is seen less commonly[38].

Multiple minute areas of erosion often spread throughout the calvarium[38,42]. These may appear as a finely granular osteoporosis[38]. Sometimes the areas of destruction are confined to the suture margins, causing an exaggeration of the spreading of the sutures (Fig. 4*C*). The areas are occasionally quite large, similar to those in other metastatic malignancies[29]. Sometimes multiple punched-out areas of destruction are present[58] like the lesions of multiple myeloma in adults. Patches of increased bone production may be seen amongst the areas of destruction in the calvarium, an appearance rather characteristic of neuroblastoma[168]. Sometimes the sella turcica is eroded[29]. Palpable soft tissue masses may appear in the scalp, and are almost invariably accompanied by underlying destruction[205].

Fine, perpendicular, radiating spicules seen in the calvarium, especially in the parietal region, have been somewhat overemphasized in the past; they occur in only a minority of cases. When present, however, they are highly suggestive of neuroblastoma[29,158].

In patients with exophthalmos and orbital ecchymoses[58], bony destruction of the orbital walls is demonstrated.

LESIONS OF THE SPINE. Multiple areas of destruction commonly develop in the spine. Osteoblastic areas of increased density may be seen in lesions of long standing in either the spine or pelvis[25,205], but they never occur without some element of destruction[168].

Following Roentgen-ray therapy of the abdomen, evidences of radiation damage may appear in the spine, due to the relatively low tolerance of the epiphyseal cartilaginous plates to irradiation. The latent interval between the radiation and the appearance of the lesions is quite long, so that the damage is seen in only the long survivors of neuroblastoma and other retroperitoneal tumors. Neuhauser *et al.*[133] found evidences of damage in 21 out of 34 children. The more severe changes tended to occur in children irradiated under the age of 2 years. One thousand to 2000 r delivered to the spine caused "transverse lines" of growth disturbance, and more than 2000 r caused irregularities of contour or scalloping of the epiphyseal plates of the vertebrae. In advanced stages, the lesions simulated the appearance of osteochondrodystrophy. Cartilaginous exostoses in the ribs and ilium sometimes appeared. When unilateral abdominal irradiation was given, the vetebrae became diminished in height on one side resulting in a scoliosis, usually of mild degree[133,153,198]. Unilateral underdevelopment of the ilium was also observed on the irradiated side[198].

CHEST LESIONS. Evidences of bony destruction of the ribs, shoulder girdles and thoracic spine may be seen on chest films. Mediastinal masses occur in 20%[168] to 27%[203] of neuroblastomas, almost always in the posterior mediastinum (Fig. 4*D*). Involvement of the mediastinum may be the primary site of origin, a metastasis, or uncommonly a direct spread of an abdominal tumor through the diaphragm[205]. Calcification within the mediastinal mass is uncommon[168], but when it occurs it should suggest neuroblastoma[176]. Less frequently, nodular metastases in the lung parenchyma, pleural effusion, and nodular pleural metastases are seen[176]. Localized areas of pleural thickening often accompany destructive rib lesions[205]. Involvement of the chest as well as the abdomen in neuroblastoma renders the prognosis very bad[203].

Non-hormonal Adreno-cortical Adenomas and Carcinomas. These non-

functioning tumors are often quite large before being diagnosed[20]. Frequently, they are discovered incidentally in various abdominal radiologic examinations[21]. The first symptoms, usually flank pain or backache[22,206], occur quite late. Rarely, the larger tumors may cause hypertension secondary to renal ischemia by compression or torsion of the renal arteries; the blood pressure may return to normal after removal of the tumor[35]. The hypertension on occasion may be even paroxysmal, simulating pheochromocytoma[156]. Cortical adenomas and carcinomas occur at any age. Although adenomas are not frequently encountered in childhood, they are the commonest benign retroperitoneal tumors of this age group[173]. Adreno-cortical carcinoma is most frequent from 30 to 50 years[31].

Calcification within the soft tissue mass may be seen on plain films of the abdomen. It is quite common in cortical carcinoma[13,62,74,93], but much less common in adenoma[13]. These tumors in childhood are frequently calcified[23,62]. Rarely, the calcifications are peripheral and ring-like, simulating the appearance of a cyst[44]. The rarer types of non-functioning adrenal tumors such as teratomas may also, on occasion, be calcified[90].

In pyelograms, the adrenal masses often displace and distort the upper renal calyces on the affected side and depress the kidney; they are often mistaken for renal tumors of the upper poles. Some of them have not been demonstrated on pyelograms, yet well demonstrated on gas insufflations; this has happened particularly in anterior tumors[20]. Larger adrenal carcinomas have sometimes failed to become outlined with the gas on an insufflation study, due to malignant infiltration into the surrounding tissues[20,180].

From 10%[31] to 20%[206] of adreno-cortical carcinomas are bilateral. In insufflation studies, however, these often appear to be unilateral, or more extensive on one side. This malignancy may spread by direct extension into the liver or into the neighboring gastrointestinal tract[13], and may be demonstrated on gastrointestinal series or barium enemas. Widespread metastases may occur to the liver, lymph nodes, lungs[156], and mediastinum[35]. Destructive lesions may appear in the pelvis[31] and elsewhere in the skeleton.

Adrenal Cysts. Adrenal cysts are quite rare; only 20 cases were found in the literature up to 1952[140]. Plain films and urographic radiologic procedures have merely demonstrated mass-like lesions in the adrenal areas[45, 140], usually depressing the kidney. A rim of peripheral calcification has been described in cystic adenomas[4,112].

Cushing's Syndrome. This type of hyperadrenalism is usually clinically distinct from the adrenogenital syndrome particularly in childhood[202]. Transitional forms of Cushing's and the adrenogenital syndrome, however, may occur after puberty[108,166], the commonest variations being the adrenogenital syndrome with obesity, and Cushing's syndrome with hirsutism. According to Kenyon[194], hyperfunction of the adrenal cortex may occasionally produce only single or isolated endocrine manifestations, rather than either of the two syndromes.

ETIOLOGY. It has been seen from the age of 3 months[202] to 78 years[43] with an average age of 34 years[43]. Only 26 cases could be collected from the literature under the age of 10 years[50,202]; all of these were due to adrenal tumors, and they were often malignant. The syndrome is four times as common in females[99], as in males, and is apparently rare in Negroes.

The administration of cortisone, ACTH, or Compound F is now a com-

mon cause of the syndrome[148]. In 98 necropsied cases collected from the literature by Knowlton[99], there were 58 diffuse adrenal hyperplasias, 31 basophilic pituitary adenomas, 24 combined diffuse adrenal hyperplasias and basophilic adenomas, 11 benign adrenal tumors, and 17 adreno-cortical carcinomas. In 9 cases, the adrenal glands were normal histologically, and 6 of these had various pituitary lesions other than basophilic adenoma. In another series of 98 necropsied cases collected by Thompson and Eisenhardt[187], the syndrome was due to a thymic tumor in 3 cases and to an arrhenoblastoma in one case. Hypothalamic lesions may rarely occur in Cushing's syndrome, and in some of these, they may be the secondary rather than the primary cause of the syndrome[99,202]. In one unusual case[98], a neuroblastoma caused pressure atrophy of the adjacent adrenal gland and hyperplasia of the opposite gland, with secondary Cushing's syndrome. Crooke's hyalinization of the pituitary basophils, formerly thought to be characteristic of Cushing's syndrome, has been found in other types of hyperadrenalism, especially in virilizing syndromes[99].

DEMONSTRATION OF ADRENAL LESIONS. By the pre-sacral gas insufflation technique, the bilateral adrenal enlargement due to hyperplasia[53] or the unilateral neoplastic enlargement due to adenoma or carcinoma[30,50] can usually be demonstrated. This examination is especially valuable when the clinical picture or biochemical findings of the syndrome are atypical[114]. In one series of 10 cases due to adrenal hyperplasia[180], the adrenals failed to visualize in 2, but a bilateral adrenal enlargement was demonstrated in the remaining 8 cases. In one case, a small hump was found on the adrenal gland due to localized hyperplasia. In another series of 29 cases, studied by pre-sacral gas insufflation and followed by surgery[99], 8 adrenal tumors were demonstrated and subsequently proven. There were no false negative diagnoses, but several false positive diagnoses of tumor in the gas studies. Some tumors have been clearly demonstrated which were not apparent on pyelograms[120]. Calcifications have been demonstrated in cortical carcinomas producing the syndrome[108].

OTHER ABDOMINAL FINDINGS. Evidences of pyelonephritis are frequently demonstrated on pyelography, due to the increased susceptibility to infections in this syndrome. The patients are also prone to develop renal calculi, especially in the presence of hypercalciuria[148,175]. The calculi are often small, multiple, and faintly radiopaque[175]. In one series of 38 patients, renal calculi were demonstrated in 35%[195]. There may also be an increased incidence of gallstones in this disease[175]. A premature calcification of the abdominal aorta has been observed in some patients[195], perhaps attributable to the diabetic-like metabolic disturbances.

GENERALIZED OSTEOPOROSIS. The excessive conversion of protein into carbohydrate due to the increased production of glycogenetic cortical steroids in this syndrome results in deficient protein anabolism and true osteoporosis[175,202]. In pathological studies[52], the osteoporosis is accompanied by abnormal thinning of the bony trabeculae without evidence of excessive bone destruction. It tends to involve the bones of the trunk and be inconspicuous or absent in the extremities; it, therefore, follows the same distribution as the obesity[175]. In a series of 61 cases collected in 1939, only 5% did not have radiological evidence of porosis; however, in an additional 8%, the osteoporsis was questionable[43]. Since then, it has become apparent that with earlier stages of the

syndrome, significant skeletal changes may be absent, even in cases of long standing[30]. In a more recent series of 38 cases[99], osteoporosis was observed in 75%. Recalcification of the porotic bone is usually not demonstrable on roentgenographic films for years after clinical recovery[195]. However, complete disappearance of marked porosis has been observed in one year's time[120].

CHANGES IN THE SPINE AND PELVIS. The generalized osteoporosis is best demonstrated in the thoracic and lumbar spine[52,99] (Fig. 5*A*). The trabeculae become thinned and diminished in number; vertical "striations" are seen in the vertebral bodies due to the accentuation of the vertical trabeculae and disappearance of the horizontal ones[195]. The end plates of the vertebrae often appear abnormally prominent in contrast to the porosis of the rest of the bodies[166,175]. The intervertebral disc spaces become expanded producing biconcave deformities of the superior and inferior plates[50]. When severe, these deformities result in the appearance of "fish" vertebrae.

Pathological compression fractures of the spine occur in about one-third of the patients[99], so that back pain is a fairly common symptom[202]. The collapse is most frequently seen in the mid-thoracic region but is also common in the lumbar spine[195]. The expansion of the intervertebral discs into the vertebral plates is usually better demonstrated in the lumbar spine.

Osteoporosis of the pelvis is seen in about one-half of the cases[195]. Uncommonly, spontaneous fractures may be observed in the ischio-pubic rami with abundant callus[195]. Rarely, acetabular protrusion may occur. In one case, multiple localized areas of rarefaction in the pelvis simulated the appearance of metastases[195].

SKULL ABNORMALITIES. Fifty[38] to 60%[144] of cases have osteoporosis of the calvarium, most marked in the frontal and parietal regions[182]. It may have the appearance of punctate granular rarefactions[195]. Rarely, a coarse granular mottling may resemble hyperparathyroidism[182]. The earliest stages of porosis are first apparent in the posterior clinoid processes and dorsum sellae[148,182]. Even when the syndrome is due to a basophilic adenoma, the tumors are usually so small that no destructive or expansile changes occur in the sella turcica. There are at least 6 cases in the literature, however, in which expansion of the sella has been observed; the changes were slight in 4 of these[114,175,195] and extensive in two[59,122].

The lamina dura of the teeth is markedly thinned and may even be absent around individual teeth. There is no uniform disappearance of the lamina dura, however.

CHEST ABNORMALITIES. The ribs are a frequent site of osteoporosis, being demonstrable in 70% in one series of 37 cases[195]. Curious pathological rib fractures occur in about 10% of patients[99] (Fig. 5*B*). These are usually multiple bilateral fractures of the lower anterior ribs, often painless and without a history of trauma[175]. Fracture lines are sometimes not visible[182]. The outstanding feature is the abundant calcified callus which surrounds the fractures with a ring-like shell[182]. It may be present when osteoporosis is not obvious radiologically[181]. The soft cotton-wool appearance of the callus formation can be mistaken for nodular lesions within the lungs, until the constant relationship to the ribs is detected. Uncommonly some enlargement of the costochondral junctions is apparent, due to minute multiple infractions[195].

Cardiac enlargement is usually demonstrated on chest films especially in long-standing cases[175], secondary to the hypertension and increased blood volume.

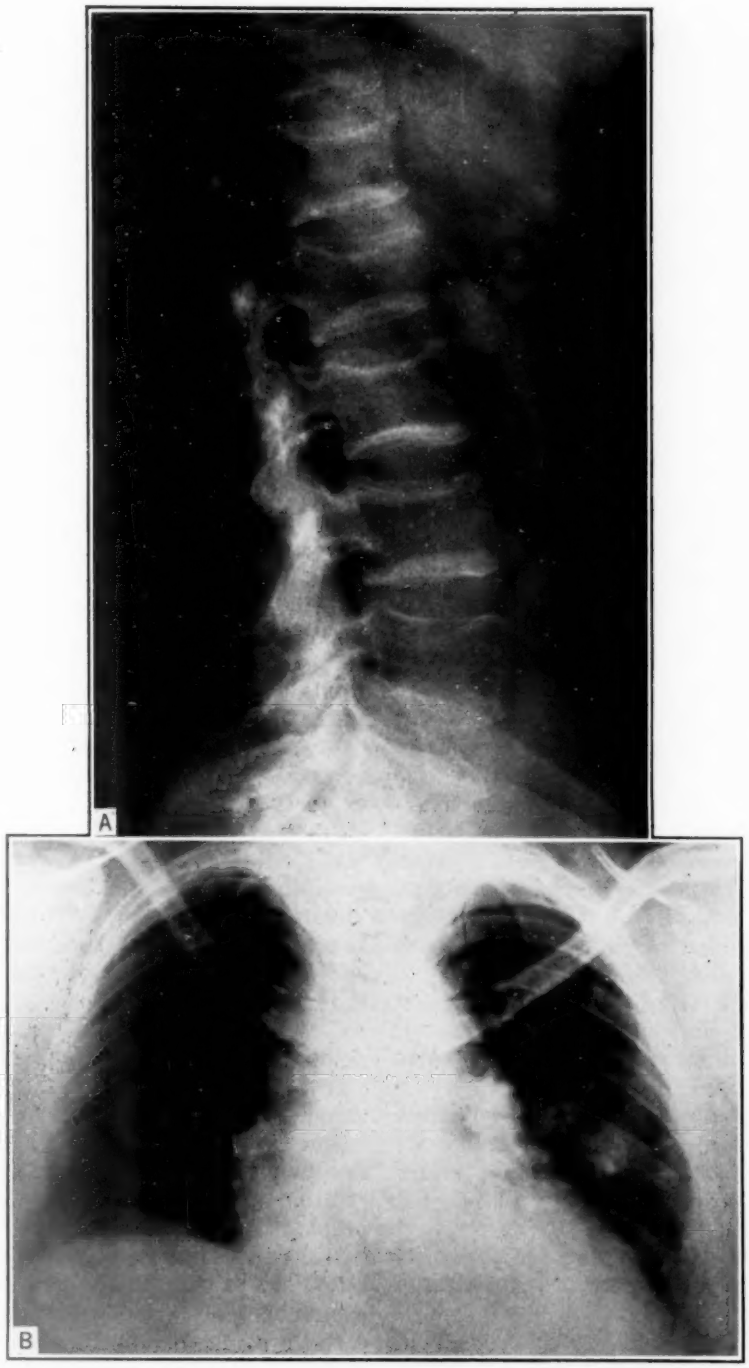


Fig. 5.—Cushing's syndrome due to adrenal hyperplasia. *A*. Marked osteoporosis of the lumbar spine is seen with collapse of the body of L-2. The superior and inferior vertebral plates are concave and abnormally prominent compared with the other rarefied structures. *B*. Chest film reveals moderate cardiac enlargement associated with hypertension, and osteoporosis of the ribs. The rounded density in the left lung field is abundant calcified callus surrounding a pathological rib fracture. Other rib fractures are present but are poorly seen.

CHANGES IN THE EXTREMITIES. In severe osteoporosis, the extremities may be involved, usually confined to the humeri and femora[182]. Pathological fractures in the extremities have rarely been observed[195]. In children, there may be delayed epiphyseal development[43,175] when severe osteoporosis is present. The retarded growth of the long bones in children contrasts with the accelerated growth of the adrenogenital syndrome[166,202].

In 2 unusual cases, calcifications of the peri-articular soft tissues of the hands were demonstrated, similar to that seen in hyperparathyroidism and hypervitaminosis D[195].

DIFFERENTIAL DIAGNOSIS OF OSTEOPOROSIS. 1. Hyperparathyroidism. The lack of involvement of the distal extremities and lack of sub-cortical bone resorption in Cushing's syndrome usually enables differentiation. A thinning or partial loss of lamina dura may occur in either condition[195], but a complete disappearance is seen only in hyperparathyroidism.

2. Post-menopausal or senile osteoporosis. The involvement of the skull and the pathological rib fractures with callus formation are not seen with these types of osteoporosis[195].

3. Adult form of osteogenesis imperfecta. This may be readily differentiated on clinical grounds and by the involvement of the extremities.

4. Multiple myeloma may occasionally produce a picture of diffuse osteoporosis and vertebral collapse rather than the more familiar multiple destructive changes.

5. Osteoporosis due to hyperthyroidism is usually readily differentiated clinically.

The Adrenogenital Syndrome. In the congenital form of this syndrome, there is pseudohermaphroditism in the female and macrogenitosomia precox in the male. The postnatal syndrome, due to adrenal hyperplasia, adenoma or cortical carcinoma, produces virilization in the female and precocity or excess virility in the male[202]. In 140 cases under 10 years of age collected by Wilkins[202], 80% occurred in females; 70% were due to congenital adrenal hyperplasia and those remaining were due to cortical tumors. In childhood, this entity was six times as common as Cushing's syndrome[202]. In an analysis of 76 hormone producing adrenocortical tumors in children, 60% had the adrenogenital syndrome[73]. In female children under the age of 10 years with the postnatal form of the syndrome, an adrenal tumor is usually found; after the age of 10, however, either hyperplasia or tumor may occur[202]. Uncommonly, in adrenal tumors, hirsutism and elevated 17-ketosteroid excretion may occur without any other signs of virilism[89].

ADRENAL LESIONS. As the congenital syndrome is invariably due to adrenal hyperplasia, the radiological demonstration of the adrenal glands is entirely unnecessary. In the postnatal syndrome, hyperplasia may be differentiated from tumor by the fall in urinary 17-ketosteroid excretion in response to cortisone therapy[202] or by the radiological demonstration of an adrenal tumor. The larger tumors may be demonstrated by pyelography[97]. Presacral gas insufflations are invaluable in demonstrating the presence of cortical tumors[20,83]. They are not as valuable in adrenal hyperplasia. Often, bilateral enlargement of the adrenal due to hyperplasia is shown[147], but the glands occasionally may appear normal in size[20,166]. At least 8 cases of the syndrome have been produced by adrenocortical carcinoma[69]; these malignant tumors producing the syndrome are sometimes quite extensive and invasive, and may be calcified[164]. In one unusual case, adrenal hyperplasia and virilism

occurred secondary to adrenal metastases from a primary renal carcinoma[184]. In another case, marked bilateral adrenal atrophy was demonstrated in the presence of virilism due to an adrenal rest tumor of the ovary[180].

THE UROGENITAL SINUS IN FEMALE PSEUDOHERMAPHRODITISM. In the female, the urogenital sinus is a congenitally persistent common passageway distal to the junction of the vagina and urethra. It is most commonly seen in female pseudohermaphroditism due to congenital adrenal hyperplasia. Its demonstration in combination with increased urinary 17-ketosteroid excretion is sufficient to make the diagnosis of congenital adrenal hyperplasia in the female[202]. Retrograde cystourethrography[51,111] in addition to cystoscopy is of considerable aid in the demonstration of the urogenital sinus. By the retrograde injection of an opaque medium through a catheter inserted into the urogenital sinus, the lumen of the sinus, the urethra, bladder, vagina, and sometimes also of the uterus and fallopian tubes may be outlined. Sometimes retrograde spilling of the medium into the peritoneal cavity occurs[139]. Usually the meatus and caliber of the urogenital sinus resemble those of a normal urethra[202]. Sometimes, however, the sinus is quite large resembling a vagina[202]. Occasionally the communication between the vagina and urethra is covered by a membrane; the abnormality, then, cannot be demonstrated radiographically. In one rare case, the vagina opened into the posterior portion of a penile urethra[202]. In another unusual case, a double urethra was present, one of which joined the vagina forming a urogenital sinus opening on the perineum; the second urethra extended through the clitoris simulating a penile urethra[61]. Rarely, a urogenital sinus may not be present in female pseudohermaphroditism[202].

A urogenital sinus may occur in all forms of hermaphroditism and pseudohermaphroditism. The appearance of the urogenital abnormalities in the cystourethrogram when considered alone is not diagnostic of the type of heterosexual development and is not even diagnostic of the sex of the patient[51]. On occasion, an injection made through a double ballooned catheter which occludes the bladder neck and urethral orifice may succeed in demonstrating the urethro-vaginal communication when an injection through a plain catheter has failed.

INTERNAL GENITAL ORGANS IN FEMALE PSEUDOHERMAPHRODITISM. Pneumoperitoneum[111] or retropneumoperitoneum[162,174] when performed in the knee-chest position may delineate the external surfaces of the uterus, fallopian tubes, and ovaries. Hypoplasia of these structures in female pseudohermaphroditism may be demonstrated.

SKELETAL CHANGES IN THE ADRENOGENITAL SYNDROME IN CHILDHOOD. Accelerated epiphyseal ossification and growth in the length of the long bones[73,111,202] are demonstrated radiologically in keeping with the marked muscular development and rapid growth in height observed clinically. Early epiphyseal fusion also may occur, causing a shortening of stature. On the basis of these skeletal findings alone, the advanced bone age of the adrenogenital syndrome is indistinguishable from that of constitutional origin.

Feminizing Adrenal Tumors: Fourteen adreno-cortical tumors producing feminization and gynecomastia in males have been collected[125]. Most of these tumors have been malignant[202]. Some have been demonstrated successfully by means of pre-sacral gas insufflation[20,125].

Pheochromocytoma. About 10% of these tumors are multiple[19] and they

are often bilateral. They are rarely familial and about 9% are malignant[19, 156]. Five per cent[37] have associated neurofibromatosis and some may be associated with other neurocutaneous syndromes[172]. Eighty-eight per cent occur in the adrenal areas, the remainder being located in the paraaortic ganglia, the organ of Zuckerkandl (sacrococcygeal body), carotid body, and thoracic sympathetic ganglia. They are relatively uncommon in childhood[186,202].

Most of these tumors are small and are the most difficult of all adrenal tumors to demonstrate radiologically. Many, however, have been demonstrated successfully by pre-sacral gas insufflation[9,53,54,65,93,186], and a few by abdominal aortography. Gas studies may be successful when more conventional radiological examinations have failed[55], but smaller tumors can never be ruled out. Even when a unilateral adrenal tumor has been demonstrated, both sides must be surgically explored[138]. Gas studies do not play as important a role in diagnosis as the provocative tests, the ganglionic blocking tests, or the quantitative estimations of the catecholamines in the urine. They are chiefly of value when the clinical picture is atypical and when the biochemical tests are negative or equivocal. They are also more applicable in patients with sustained hypertension, because false negatives have occurred with the ganglionic blocking tests[55]. In the diagnosis of pheochromocytomas in children who are apt to have sustained hypertension or diabetic-like symptoms, gas studies may aid in diagnosis[186].

A few pheochromocytomas have radiologically detectable calcification[17, 60,66] in areas of hemorrhage and necrosis. Ring-like calcification, simulating the appearance of a gallstone, has been observed[127]. Few of these tumors are large enough to be palpated clinically[138]; only about 20% are demonstrable by pyelography[147]. Paragangliomas, arising from the lumbar sympathetic ganglia, when lying medial to the kidneys, may distort the renal pelvis[180] and displace the kidney laterally[10]. Pre-sacral gas insufflation studies may also demonstrate these tumors[10,197]. The rare tumors arising from thoracic sympathetic ganglia have presented radiologically as mediastinal masses[116,129]

Primary Aldosteronism: (Conn's Syndrome). The excessive production of aldosterone by the adrenal cortex, resulting in excessive sodium retention, potassium diuresis, and secondary alkalosis is sometimes due to a primary adrenal lesion. The primary type of aldosteronism has occurred in adrenal cortical adenoma, carcinoma, and bilateral adrenal hyperplasia. In 30 of Conn's[32] cases of aldosteronism, 10 were due to adrenal tumors and one was due to hyperplasia. Little is known about the radiological changes in this syndrome, but pre-sacral gas insufflation has been used for the demonstration of the adrenal tumors[28].

Acute Adrenal Insufficiency. Diagnostic radiology plays no useful role in the diagnosis of acute adrenal insufficiency. In infantile adrenal insufficiency, either primary[92,155,196] or secondary to adrenal hyperplasia[128], the clinical picture may closely simulate pyloric obstruction with projectile vomiting and gastric distention[128]. Radiologically, these cases have presented with gaseous distention of the stomach and a complete absence of gas in the remainder of the gastrointestinal tract. There may be marked delay in the passage of barium through the pylorus[196]. This "pseudo-pyloric stenosis," therefore, may mimic pyloric obstruction radiologically as well as clinically. Sometimes the distention occurs in the duodenal bulb in addition to the

stomach, thereby simulating the radiological appearance of congenital duodenal atresia[196]. The disturbances in bowel function in infantile adrenal insufficiency are entirely reflex in origin. Because these findings have not been appreciated, several infants have been subjected to surgery.

Addison's Disease. Chronic adrenal insufficiency has occurred at all ages from infancy[39] to late adulthood[91], although it is rare under the age of 5 years[202]. In one series of 120 cases, there was no significant sex predominance[91]. In older necropsy series, 70% of all cases of Addison's disease were due to tuberculosis, the remainder usually being due to idiopathic cortical necrosis and atrophy. In recent years, however, the proportion of cases due to tuberculosis is steadily decreasing. Some cases have been due to histoplasmosis.

In a series of 59 cases in children under the age of 15[92], 90% were due to tuberculosis as established at postmortem examination; the others were due to adrenal atrophy. In the rare instances occurring in infancy and early childhood, the disease is almost always due to atrophy or hypoplasia[171]: cases were reported, however, in which the disease was due to adrenal cysts[123] and to previous traumatic adrenal hemorrhage[39].

DEMONSTRATION OF ADRENAL ATROPHY. Pre-sacral gas insufflation studies have shown diminution in size of the adrenal shadows[8]. These studies, however, are entirely unnecessary for diagnosis. Furthermore, the diagnosis of an abnormal decrease in size of the adrenals must be made with caution, because of wide normal variations[115]. In one case, the adrenal gland had a normal configuration on a gas study, yet at postmortem examination was atrophic and functionless[20].

ADRENAL CALCIFICATION. This is an important finding in Addison's disease[157,189]. It is better seen on plain films of the abdomen than in gas studies[115] (Fig. 6A). For detecting and localizing very minimal calcifications, mild oblique projections are invaluable[6,88] but laminography is not particularly helpful[91]. This finding is seen radiologically in about 25% of all cases of Addison's disease[24,91]; in about half of the cases it is unilateral[11,91]. In postmortem radiographs of the removed adrenal glands, calcium is demonstrable in about 32%[24]. The calcifications are usually multiple, discrete, and minute, but occasionally there is a single large nodule and rarely there is a homogeneous increase in density of the gland[24].

In the differential diagnosis of adrenal calcifications, the following lesions should be considered: calcified costal cartilages, para-aortic mesenteric lymph nodes, tuberculous lesions of the upper renal poles, para-vertebral or perinephric abscesses, calcification of the abdominal aorta and its upper branches, and calculi in the upper kidneys, pancreas or gallbladder[11,24,93].

Unilateral or bilateral adrenal calcifications may be seen in the absence of Addison's disease[91]. Whenever this is accidentally found, however, Addison's disease should be ruled out. Calcifications are not uncommon in infants, due to bilateral adrenal hemorrhage[150], and may occur in infants or children without clinical manifestations[170]. It has been seen bilaterally in Niemann-Pick disease[2].

OTHER ABDOMINAL RADIOLOGICAL FINDINGS. Despite the frequent gastrointestinal complaints and frequent gastrointestinal series performed on patients with Addison's disease, peptic ulcers are quite rare before specific treatment is instituted[46,91]. In a few untreated patients, superficial gastric ulceration has been demonstrated radiologically which

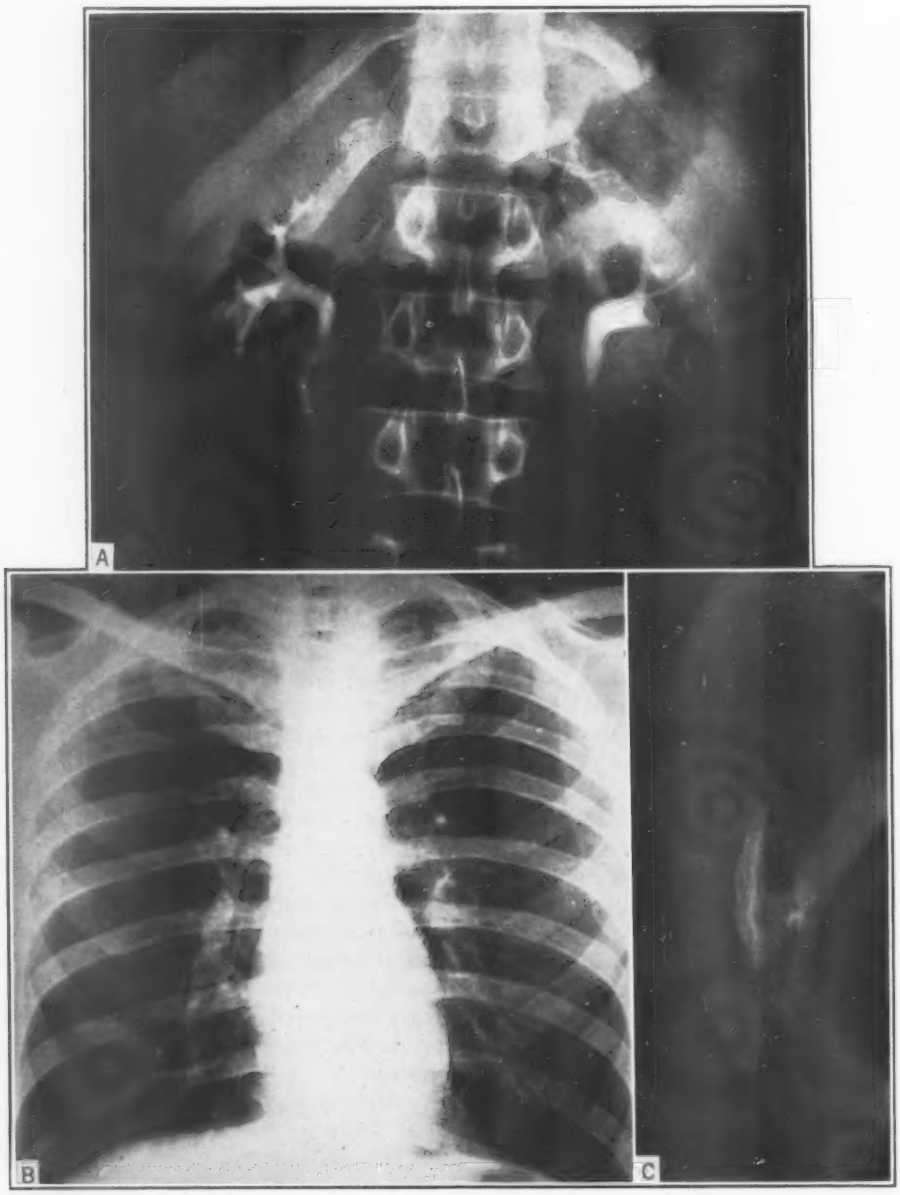


Fig. 6.—Addison's disease. *A*. Bilateral adrenal calcifications are shown on intravenous urogram. *B*. Chest film reveals minimal bilateral upper lobe tuberculosis and an abnormally small heart shadow. *C*. Soft tissue film of the external ear shows abnormal calcifications.

has cleared up under steroid therapy[91].

In female patients with Addison's disease, the kidneys often appear smaller than normal[91]. About 5% of all patients have renal tuberculosis as demonstrated by pyelography[91].

About 9% of cases show slight to moderate splenomegaly[91] on abdominal films. The spleen may become reduced in size under cortisone therapy. Splenomegaly is demonstrated in about 25% of cases at postmortem examination[160]; it appears to be merely part of the generalized hyperplasia of the lymphatic tissues seen in this disease.

ABNORMAL FINDINGS IN THE CHEST. A small heart size is invariably present in untreated Addison's disease uncomplicated by cardiac disease, due to the hypotension, low pulse pressure and diminished blood volume[91] (Fig. 6*B*). Institution of specific therapy is followed by a gradual return of the heart size to normal. A few cases have been observed, however, in which the heart has failed to increase to its normal size despite satisfactory clinical response. Excessive doses of desoxycorticosterone may give rise to cardiac enlargement. In untreated Addison's disease with a normal sized or enlarged heart, hyperthyroidism or cardiac disease must be suspected. When the disease is complicated by an organic cardiac lesion, the cardiac enlargement may be minimized but appear promptly after desoxycorticosterone therapy[91].

In cases of Addison's disease due to tuberculosis, the primary lesion may be demonstrated in the lung fields. In one series of 120 cases, only 8% had active pulmonary tuberculosis[91]. In those with adrenal calcifications, however, 54% had evidence of pulmonary tuberculosis and 29% had active lesions[91].

An increased incidence and severity of costal cartilage calcifications, compared with normal persons of similar age group have been observed in Addison's disease, but this is of no value diagnostically[91].

SKELETAL ABNORMALITIES. Six per cent of patients have evidence of tuberculosis involving the skeleton[91], usually in the spine or hips. Skull films should be routine part of the investigation to rule out the presence of a pituitary tumor as a cause of chronic adreno-cortical insufficiency. The incidence of dental caries in this disease is quite high, as demonstrated on dental films.

CALCIFICATION OF THE EARS. Calcification of the pinnae of the ears is quite common as detected by soft tissue films (Fig. 6*C*). There may be stiffness of the pinnae on palpation. In the presence of calcification of the ears, Addison's disease must be ruled out. It may, however, also occur in ochronosis (alkaptonuria)[119,145], acromegaly[132], in old hematomas in boxers and wrestlers, and rarely in the collagen vascular diseases.

Conclusion. The radiological findings which have occurred in the various adrenal diseases (nonfunctioning tumors, hyperadrenalism, and adrenal insufficiency) have been discussed. As our knowledge of these diseases has increased, it has become more apparent that they may produce a wide variety of lesions throughout the body.

Until such time as a specific contrast medium is developed for visualization of the adrenal glands, the most accurate method will remain the pre-sacral insufflation of carbon dioxide used in conjunction with intravenous pyelography and tomography. The future use of abdominal aortography in the diagnosis of adrenal lesions will probably be limited; it still may be valuable, however, for the demonstration of small vascular tumors.

REFERENCES

(1) **Aitken, S. G.:** New Zealand Med. J., **41**, 209, 1942. (2) **Alexander, W. S.:** Ibid., **45**, 43, 1946. (3) **Andersen, P. E.:** Acta radiol., **43**, 289, 1955. (4) **Anderson, M. X., Roberts, H. G.,** and **Smith, E. T.:** Radiology, **54**, 236, 1950. (5) **Anderson, O. W.:** A.M.A. Am. J. Dis. Child., **83**, 782, 1952.

(6) **Ball, R. G., Greene, C. H., Camp, J. D.,** and **Rowntree, L. G.:** J. Am. Med. Assn., **98**, 954, 1932. (7) **Barden, R. P.:** Am. J. Roentgenol., **50**, 575, 1943. (8) **Baronchelli, A.,** and **Rossi, L.:** Ann. radiol. diag., **27**, 261, 1954. (9) **Beer, E., King, F. H.,** and **Prinzmetal, M.:** Ann. Surg., **106**, 85, 1937. (10) **Berry, J. F., Robbins, J. L.,** and **Pirkey, E. L.:** A.M.A. Arch. Surg., **70**, 173, 1955. (11) **Beutel, A.:** Med. Klin., **30**, 1450, 1934. (12) **Blackwood, J.:** Brit. J. Surg., **39**, 111, 1951. (13) **Boice, C. L.,** and **Sears, W. N.:** Radiology, **56**, 731, 1951. (14) **Boyd, R. W.:** Canadian Med. Assn. J., **63**, 153, 1950. (15) **Budniok, R.:** Fortschr. a. d. Geb. d. Röntgenstrahlen, **74**, 348, 1951. (16) **Buetti-Bäuml, C.:** Radiol. clin., **21**, 225, 1952.

(17) **Cadman, E. F. B.,** and **Tinckler, L. F.:** J. Fac. Radiol., London, **4**, 211, 1953. (18) **Cahill, G. F.:** J. Urol., **34**, 238, 1935. (19) Idem: Ibid., **67**, 779, 1952. (20) Idem: Radiology, **37**, 533, 1941. (21) **Cahill, G. F., Loeb, R. F., Kurzrok, R., Stout, A. P.,** and **Smith, F. M.:** Surg., Gynec., & Obst., **62**, 287, 1936. (22) **Cahill, G. F., Melicow, M. M.,** and **Darby, H. H.:** Surg., Gynec., & Obst., **74**, 281, 1942. (23) **Cahill, G. F.,** and **Robinson, J. N.:** J. Urol., **61**, 680, 1949. (24) **Camp, J. D., Ball, R. G.,** and **Greene, C. H.:** Am. J. Roent., **28**, 594, 1932. (25) **Campbell, M.:** Clinical Pediatric Urology. Philadelphia: W. B. Saunders Co., Chapter 9, The Adrenals, 1951, p. 745. (26) **Carelli, H. H.:** Bull. et mém. Soc. méd. hôp. Paris, **45**, 1409, 1921. (27) **Carelli, H. H.,** and **Sordelli, E.:** Rev. Asoc. méd. Argent., **34**, 424, 1921. (28) **Chalmers, T. M., Fitzgerald, M. G., James, A. H.,** and **Scarborough, H.:** The Lancet, **1**, 127, 1956. (29) **Chont, L. K.:** Am. J. Roent., **46**, 809, 1941. (30) **Cleroux, A. P.,** and **Oppenheim, D. J.:** Bull. New England Med. Center, **13**, 31, 1951. (31) **Cleveland, M.,** and **Knox, L. C.:** A.M.A. Arch. Surg., **47**, 192, 1943. (32) **Conn, J. W.:** A.M.A. Arch. Int. Med., **97**, 135, 1956. (33) **Conn, J. W.,** and **Louis, L. W.:** Ann. Int. Med., **44**, 1, 1956. (34) **Cope, O.,** and **Schatzki, R.:** A.M.A. Arch. Int. Med., **64**, 1222, 1939. (35) **Cottler, Z. R.:** J. Urol., **60**, 363, 1948. (36) **Crooke, A. C.,** and **Callow, R. K.:** Quart. J. Med., **8**, 233, 1939.

(37) **Davis, F. W., Hull, J. G.,** and **Vardell, J. C.:** Am. J. Med., **8**, 131, 1950. (38) **Doub, H. P.:** J. Am. Med, Assn., **109**, 1188, 1937. (39) **Drucker, V.,** and **Rodriquez, C. E.:** Radiology, **64**, 258, 1955. (40) **Duff, J., Kenyon, H. R.,** and **Hyman, R. M.:** J. Urol., **70**, 963, 1953. (41) **Durant, T. M., Long, J.,** and **Oppenheimer, M. J.:** Am. Heart J., **33**, 269, 1947.

(42) Editorial: Radiology, **45**, 75, 1945. (43) **Eisenhardt, L. E.,** and **Thompson, K. W.:** Yale J. Biol. & Med., **11**, 507, 1939. (44) **Elkeles, A.:** Brit. J. Rad., **24**, 408, 1951. (45) **Ellis, F. H., Dawe, C. J.,** and **Clagett, O. T.:** Ann. Surg., **136**, 217, 1952. (46) **Engel, F. L.:** J. Clin. Endo. & Metab., **15**, 1300, 1955. (47) **Engel, W. J.:** A.M.A. Arch. Surg., **70**, 156, 1955. (48) **Evans, A. T.:** A.M.A. Arch. Surg., **70**, 191, 1955.

(49) **Fagerberg, S.:** Acta radiol., **37**, 519, 1952. (50) **Farber, J. E., Gustina, F. J.,** and **Postoloff, A. V.:** A.M.A. Am. J. Dis. Child., **65**, 593, 1943. (51) **Finby, N., Baker, D. H., Paquin, A. J.,** and **Evans, J. A.:** To be published. (52) **Follis, R. H., Jr.:** Bull. Johns Hopkins Hosp., **88**, 440, 1951. (53) **Fontaine, R., Warter, P., Frank, P.,** and **Raber, R.:** J. Radiol. et electrol., **32**, 427, 1951. (54) **Forrest, S. J.,** and **Goldberg, L.:** J. Canad. Assn. Radiologists, **5**, 36, 1954. (55) **Forsgren, A. L., Nesset, W. D.,** and **Anderson, D. M.:** Minnesota Med., **32**, 170, 1949. (56) **Franciosi, A. U., Govoni, A. F.,** and **Pasquinelli, C. G.:** Am. J. Roent., **72**, 1034, 1954. (57) **Frazier, H. M.:** J. Am. Med. Assn., **158**, 923, 1955. (58) **Fulton, H.,** and **Evans, W. A.:** A.M.A. Arch. Surg., **70**, 178, 1955. (56) **Furtado, D.,** and **Morato, X.:** Presse med., **47**, 1632, 1939.

(60) **Ganem, E. J.,** and **Cahill, G. F.:** New England J. Med., **238**, 692, 1948. (61) **Ganem, E. J., Wallwork, D. W.,** and **West, G. V.:** New England J. Med., **254**, 552, 1956. (62) **Garrett, R. A.:** J. Urol., **66**, 477, 1951. (63) **Gellerstedt, N.,** and **Hjelm, R.:**

Upsala lakaref. Forh., **34**, 271, 1928. (**64**) **Gennes, L. de, May, J. P.,** and **Hélie, J.:** Le Pneumo-Rétro-Péritoine. Paris: Masson et Cie, 1952. (**65**) **Gianturco, C.,** and **Drenckhahn, C. H.:** Radiology, **30**, 500, 1938. (**66**) **Gimlette, T. M. D.,** and **Swan, H. J. C.:** Proc. Roy. Soc. Med., **44**, 411, 1951. (**67**) **Godlowski, Z. Z.:** J. Fac. Radiol., **5**, 148, 1953, London. (**68**) **Golden, R.,** and **Abbott, H.:** Am. J. Roent., **30**, 641, 1933. (**69**) **Goldstein, A. E., Rubin, S. W.,** and **Askin, J. A.:** A.M.A. Am. J. Dis. Child., **72**, 563, 1946. (**70**) **Goldstein, H. M.:** A.M.A. Am. J. Dis. Child., **78**, 260, 1949. (**71**) **Goodwin, W. E., Moore, E. V.,** and **Peirce, E. C.:** J. Urol., **74**, 231, 1955. (**72**) **Gould, D. M.,** and **Willson, J. K. V.:** Am. J. Med. Sci., **228**, 586, 1954. (**73**) **Greenblatt, R. B., Chaney, R. H.,** and **Clark, S. L.:** Am. Surg., **17**, 760, 1951. (**74**) **Griffiths, E.:** Brit. J. Surg., **37**, 311, 1949–50. (**75**) **Gross, R. E.:** Surgery of Infancy and Childhood. Philadelphia: W. B. Saunders Co., 1953. (**76**) **Grunow, O. H.:** Radiology, **65**, 200, 1955.

(77) **Hamm, F. C.,** and **Harlin, H. C.:** J. Urol., **70**, 318, 1953. (**78**) **Hamm, F. C.,** and **Scordamaglia, L. J.:** Ibid., **73**, 885, 1955. (**76**) **Hansen, P. B.:** Acta radiol., **40**, 500, 1953. (**80**) **Harrison, F. G., Warres, H. L.,** and **Fust, J. A.:** J. Urol., **63**, 598, 1950. (**81**) **Harrow, B. R.:** J. Florida Med. Assn., **42**, 732, 1956. (**82**) **Haubrich, R.,** and **Thurn, P.:** Fortschr. a. d. Geb. d. Röntgenstrahlen, **78**, 719, 1953. (**83**) **Hodge, K. E.:** Brit. J. Radiol., **26**, 147, 1953. (**84**) **Holmes, G. W.,** and **Dresser, R.:** J. Am. Med. Assn., **91**, 1246, 1928. (**85**) **Hutchinson, R.:** Quart. J. Med., **1**, 33, 1907. (**86**) **Hyman, A.,** and **Mencher, W. H.:** J. Urol., **49**, 755, 1943. (**87**) **Hyman, A.,** and **Wilhelm, S. F.:** Ibid., **40**, 737, 1938.

(88) **Ingram, F. L.:** Brit. J. Rad., **23**, 232, 1950.

(89) **Jailer, J. W., Gold, J. J.,** and **Cahill, G. F.:** Am. J. Obst. & Gynec., **67**, 201, 1954. (**90**) **Jansson, G.:** Acta radiol., **27**, 526, 1946. (**91**) **Jarvis, J. L., Jenkins, D., Sosman, M. C.,** and **Thorn, G. W.:** Radiology, **62**, 16, 1954. (**92**) **Jaudon, J. C.:** J. Pediat., **28**, 737, 1946. (**93**) **Joelson, J. J., Persky, L.,** and **Rose, F. A.:** Radiology, **62**, 488, 1954.

(94) **Kaplan, J. H.,** and **Greene, L. F.:** S. Clin. N. America, **28**, 1071, 1948. (**95**) **Karsner, H. T.:** Atlas of Tumor Pathology, Section VIII. Fascicle 29: Tumors of the Adrenal. Washington. D.C.: Publ. Armed Forces Inst. of Path., 1950. (**96**) **Kearns, W. M.:** Wisconsin Med. J., **53**, 139, 1954. (**97**) **Kiefer, J. H.,** and **Bronstein, I. P.:** J. Urol., **62**, 639, 1949. (**98**) **Kis-Várday, G.:** Fortschr. a. d. Geb. d. Röntgenstrahlen, **82**, 610, 1955. (**99**) **Knowlton, A. I.:** Bull. New York Acad. Med., **29**, 441 ,1953. (**100**) **Kokas, F.,** and **Zsebök, Z.:** Fortschr. a. d. Geb. d. Röntgenstrahlen, **74**, 218, 1951. (**101**) **Koonce, D. H., Pollock, B. E.,** and **Glassy, F. J.:** Am. Heart J., **44**, 901, 1952. (**102**) **Koop, C. E., Kiesewetter, W. M.,** and **Horn, R. C.:** Surgery, **38**, 272, 1955. (**103**) **Kouyoumdjian, A. O.,** and **McDonald, J. J.:** Cancer, **4**, 784, 1951. (**104**) **Kraus, S.:** J. Am. Med. Assn., **143**, 132, 1950.

(105) **Lederer, M.:** J. Cancer Res., **10**, 377, 1926. (**106**) **Lefebvre, J., Sauvegrain, J., Faure, C., Guy, E.,** and **Bisson, A.:** J. de radiol. et d'electrol. & Arch. d'electric. med. **34**, 483, 1953. (**107**) **Lerman, F., Harper, J. G. M., Hertzberg, A. D., Berman, M. H.,** and **Lerman, P. H.:** J. Urol., **70**, 312, 1953. (**108**) **Lescher, F. G.:** Quart. J. Med., **4**, 23, 1935. (**109**) **Levin, B.:** J. Urol., **67**, 390, 1952. (**110**) **Levin, E. B.:** A.M.A. Arch. Int. Med., **92**, 906, 1953. (**111**) **Levin, B., Rambar, A. C.,** and **Shapiro, I. J.:** Am. J. Roent., **69**, 948, 1953. (**112**) **Levison, P.:** Endocrinology, **17**, 372, 1933. (**113**) **Lintz, W.:** J. Am. Med. Assn., **121**, 505, 1943. (**114**) **Lisser, H.:** J. Clin. Endo. & Metabl., **15**, 1144, 1955. (**115**) **Lurá, A., Forni, G.,** and **Biavati, C.:** Ann. radiol. diag., **27**, 298, 1954.

(116) **Maier, H. C.:** Ann. Surg., **130**, 1059, 1949. (**117**) **Mandeville, F. B.:** Urol. & Cutan. Rev., **51**, 448, 1947. (**118**) Idem: Radiology, **53**, 403, 1949. (**119**) **Martin, W. J., Underdahl, L. O., Mathieson, D. R.,** and **Pugh, D. G.:** Ann. Int. Med., **42**, 1052, 1955. (**120**) **McLaughlin, W. L.,** and **Bowler, J. P.:** J. Urol., **58**, 221, 1947. (**121**) **Messenger, H. M.,** and **Monroe, L.:** Gastroenterology, **29**, 313, 1955. (**122**) **Messimy, R., Berthet, G.,** and **Cousin, R.:** Rev. neurol., **82**, 273, 1950. (**123**) **Moore, F. P.,** and **Cermak, E. G.:** J. Pediat., **36**, 91, 1950. (**124**) **Moos, F. von:** Schweiz. med. Wchnschr., **82**, 629, 1952. (**125**) **Mortensen, H.,** and **Murphy, L.:** J. Urol., **65**, 709, 1951. (**126**) **Mosca, L. P.:** (Quoted by **Steinbach, H. L., Lyon, R. P., Smith, D. R.,** and **Miller, E. R.**) Radiology, **59**, 167, 1952. (**127**) **Moser, M., Sheehan, G.,** and **Schwinger, H.:** Radiology, **55**, 855, 1950. (**128**) **Munck, W.:**

Acta path. et microbiol. scandiav. suppl. 91, **24**, 1951. (**129**) **Murray, M. R.**, and **Stout, A. P.**: Am. J. Path., **23**, 429, 1947. (**130**) **Musgrove, J. E.**, and **Mac Quigg, R. E.**: J. Am. Med. Assn., **150**, 28, 1952. (**131**) **Myerson, R. M.**, and **Wohl, G. T.**: Am. J. Med., **19**, 155, 1955.

(**132**) **Nathanson, L.**, and **Losner, S.**: Radiology, **48**, 66, 1947. (**133**) **Neuhauser, E. B. D., Wittenborg, M. H., Berman, C. Z.**, and **Cohen, J.**: Radiology, **59**, 637, 1952. (**134**) **Newsam, A. R.**: Rhode Island Med. J., **7**, 35, 1924. (**135**) **Nice, C. M., Margulis, A. R.**, and **Rigler, L. G.**: Am. J. Roent., **75**, 977, 1956. (**136**) **Nichols, F. L., Root, S. A., Mirabile, C. S.**, and **Lampson, R. S.**: New England J. Med., **247**, 11, 1952.

(**137**) **Oddo, V. J.**: J. Urol., **55**, 1, 1946. (**138**) **Orgain, E. S.**: Ann. Int. Med., **43**, 1178, 1955.

(**139**) **Panos, T. C.**: Pediatrics, **5**, 972, 1950. (**140**) **Parker, D.**: J. Urol., **68**, 1, 1952. (**141**) **Parsons, P. B.**, and **Platt, L.**: Am. J. Roent., **44**, 175, 1940. (**142**) **Pepper, W.**: Am. J. Med. Sci., **71**, 287, 1901. (**143**) **Phillips, R.**: Ann. Roy. Coll. Surg., England, **12**, 29, 1953. (**144**) **Plotz, C. M., Knowlton, A. I.**, and **Ragan, C.**: Am. J. Med., **13**, 597, 1952. (**145**) **Pomeranz, M. M., Friedman, L. J.**, and **Tunick, I. S.**: Radiology, **37**, 295, 1941. (**146**) **Potter, E. L.**, and **Parrish, J. M.**: Am. J. Path., **18**, 141, 1942. (**147**) **Poutasse, E. F.**: J. Urol., **73**, 891, 1955. (**148**) **Poutasse, E. F.**, and **McCullagh, E. P.**: Ibid., **68**, 779, 1952.

(**149**) **Quinby, W. C.**: Ibid., **9**, 13, 1923.

(**150**) **Rack, F. J.**, and **Eiben, R. M.**: J. Ped., **39**, 618, 1951. (**151**) **Ransom, C. L.**: To be published. (**152**) **Reese, L.**, and **MacLean, J. T.**: Canad. Med. Assn. J., **67**, 632, 1952. (**153**) **Reiquam, C. W., Beatty, E. C., Jr.**, and **Allen, R. P.**: A.M.A. Am. J. Dis. Child., **91**, 588, 1956. (**154**) **Renter, H. R.**: Radiol. clin., **22**, 29, 1953. (**155**) **Roberts, M. H.**, and **Baehren, P. F.**: J. Med. Assn. Georgia, **41**, 299, 1952. (**156**) **Robinson, P. L.**, and **Baker-Bates, E. T.**: Brit. J. Surg., **41**, 399, 1954. (**157**) **Rolleston, H. D.**, and **Boyd, E. J.**: Brit. J. Child. Dis., **11**, 105, 1914. (**158**) **Rosendal, T.**: Acta radiol., **23**, 462, 1942. (**159**) **Rothfield, S. H., Hamm, F. C.**, and **Harlin, H. C.**: J. Urol., **69**, 721, 1953. (**160**) **Rowntree, L. G.**, and **Snell, A. M.**: A Clinical Study of Addison's Disease. Philadelphia: W. B. Saunders Co., 1931. (**161**) **Ruiz Rivas, M.**: Rev. clinica españ., **25**, 206, 1947. (**162**) Idem: Am. J. Roent., **64**, 723, 1950. (**163**) **Russ, F. H., Glenn, D. L.**, and **Gianturco, C.**: Radiology, **61**, 637, 1953.

(**164**) **Samuel, E.**: Brit. J. Rad., **21**, 139, 1948. (**165**) **Saphir, O.**, and **Parker, M. L.**: A.M.A. Arch. Surg., **42**, 1003, 1941. (**166**) **Schinz, H. R., Baensch, W. E., Friedl, E.**, and **Uehlinger, E.**: Roentgen Diagnostics. New York: Grune & Stratton, 1954. 1st American Edition edited by **Case, J. T.**, Vol. II, p. 1168. Vol. IV, p. 3767. The Suprarenal Glands. (**167**) **Schulte, T. L.**, and **Emmett, J. H.**: J. Urol., **42**, 215, 1934. (**168**) **Sherman, R. S.**, and **Leaming, R.**: Radiology, **60**, 837, 1953. (**169**) **Smith, D. R., Steinbach, H. L., Lyon, R. P.**, and **Stratte, P. B.**: J. Urol., **68**, 953, 1952. (**170**) **Snelling, C. E.**, and **Erb, I. H.**: J. Pediat., **6**, 22, 1935. (**171**) Idem: Ibid., **7**, 699, 1935. (**172**) **Snyder, C. H.**, and **Rutledge, L. J.**: Pediatrics, **15**, 312, 1955. (**173**) **Snyder, W. H., Kruse, C. A., Greaney, E. M.**, and **Chaffin, L.**: A.M.A. Arch. Surg., **63**, 26, 1951. (**174**) **Sommer, F.**, and **Reinhardt, K.**: Fortschr. a. d. Geb. d. Röntgenstrahlen, **77**, 54, 1952. (**175**) **Sosman, M. C.**: Am. J. Roent., **62**, 1, 1949. (**176**) **Startz, I. S.**, and **Abrams, J.**: Radiology, **30**, 232, 1938. (**176a**) **Stauffer, H. M., Durant, T. M.**, and **Oppenheimer, M. J.**: Ibid., **66**, 686, 1956. (**177**) **Steinbach, H. L.**, and **Brown, R. F.**: Calif. Med., **78**, 263, 1953. (**178**) **Steinbach, H. L., Lyon, R. P., Miller, E. R.**, and **Smith, D. R.**: Ibid., **75**, 202, 1951. (**179**) **Steinbach, H. L., Lyon, R. P., Smith, D. R.**, and **Miller, E. R.**: Radiology, **59**, 167, 1952. (**180**) **Steinbach, H. L.**, and **Smith, D. L.**: A.M.A. Arch. Surg., **70**, 161, 1955. (**181**) **Strickland, B.**: Proc. Roy. Soc. Med., **47**, 341, 1954. (**182**) **Sussman, M. L.**, and **Copleman, B.**: Radiology, **39**, 288, 1942.

(**183**) **Tahka, H.**: Acta ped., **40**, suppl. 81, 1951. (**184**) **Tenenbaum, J.**: Am. J. Surg., **52**, 120, 1941. (**185**) **Teschendorf, W.**: Acta radiol., **36**, 297, 1951. (**186**) **Tevetoglu, F.**, and **Chi-Hao Lee**: A.M.A. Am. J. Dis. Child., **91**, 365, 1956. (**187**) **Thompson, K. W.**, and **Eisenhardt, L.**: J. Clin. Endo., **3**, 445, 1943. (**188**) **Thompson, R. M.**: Ann. Int. Med., **16**, 1206, 1942. (**189**) **Thompson, T.**: Lancet, **2**, 785, 1930. (**190**) **Tinckler, L. F.**: J. Fac. Rad., **4**, 268, 1953.

(191) **Uhlmann, E. M.,** and **Essen, C. von:** Pediatrics, **15,** 402, 1955.
(192) **Vespignani, L.:** Acta radiol., **36,** 509, 1951.
(193) **Walter, R. C.,** and **Goodwin, W. E.:** J. Urol., **70,** 526, 1953. (**194**) **Walters, W.,** and **Sprague, R. G.:** J. Am. Med. Assn., **141,** 653, 1949. (**195**) **Wang, C. C.,** and **Robbins, L. L.:** Radiology, **67,** 17, 1956. (**196**) **Weens, H. S.,** and **Golden, A.:** Am. J. Roent., **74,** 213, 1955. (**197**) **Weiman, C. G., Back, K., Russo, P. E., Shoemaker, H. A.,** and **Wolf, S.:** Ann. Int. Med., **41.** 131, 1954. (**198**) **Whitehouse, W. M.,** and **Lampe, I.:** Am. J. Roent., **70,** 721, 1953. (**199**) **Wilhelm, S. F.:** J. Urol., **49,** 785, 1943. (**200**) Idem: Brit. J. Urol., **19,** 85, 1947. (**201**) Idem: Surg., Gynec., & Obst., **99,** 319, 1954. (**202**) **Wilkins, L.:** The Diagnosis and Treatment of Endocrine Disorders in Childhood and Adolescence. Springfield, Ill.: Charles C Thomas, 1953, Chap. XII, (Pt. I) Adrenal Cortex. I. Hormones and Their Actions, p. 202. (**203**) **Wittenborg, M. H.:** Radiology, **54,** 679, 1950. (**204**) **Wood, J. C.:** Brit. J. Rad., **25,** 222, 1952. (**205**) Wyatt, **G. M.,** and **Farber, S.:** Am. J. Roent., **46,** 485, 1941.
(206) **Zaslow, J.,** and **Bernstein, M.:** J. Urol., **54,** 409, 1945.

SUMMARIO IN INTERLINGUA

(See page 504 for original article)

Le Dynamica del Therapia a Medication Ficticie: Un Studio Clinic

1. Septanta-cinque patientes con symptomas psychosomatic esseva dividite in tres gruppos quasi equal. Gruppo A recipeva un potente pillula que deprimeva le systemas nervose autonomic e central. Gruppo B recipeva un medication ficticie. Gruppo O recipeva nulle medication pillular. Le subjectos in omne tres gruppos recipeva psychotherapia de orientation analytic. Le investigatores ignorava qual pillulas esseva potente e quales esseva le medication ficticie.

2. Le resultatos esseva registrate per e le patiente e le medico. Le gruppo a pillulas potente e le gruppo a medication ficticie non esseva differentiabile per lor numeros de patientes meliorate. Le gruppo que recipeva psychotherapia e nulle medication habeva le plus alte numero de patientes meliorate. Le majoritate del patientes reageva emotivemente al pillulas potente e al medication ficticie.

3. Le medication ficticie pote esser non importa qual substantia que es administrate con intentiones therapeutic. Le medication ficticie pote evocar o non evocar un "reaction a medication ficticie" de character subjective o objective, psychologic o physiologic, positive o negative. Le "reaction a medication ficticie" non ha un psychiatric signification diagnostic.

4. Le "potentia" del medication ficticie depende del relation inter patiente e medico. Illo es un parte de iste relation con su base emotional. Su potentialitate es restringite per le confinios del psychotherapia practic. Le majoritate del patientes progredeva melio in nostre tractamento sin le uso de ulle medication ficticie. Le "reaction a medication ficticie" occurre in psychotherapia, mesmo sin pillula, in le si-appellate curation per "transferentia" affective. Indicationes specific pro therapia a medication ficticie es non ancora disponibile, sed medication ficticie deberea esser acceptate como adjuncto al psychotherapia.

5. Nos conclude que therapia a medication ficticie debe esser le secreto del therapeuta, que un substantia que ha le possibilitate de influentiar le un o le altere symptoma somatic debe esser usate como medication ficticie, e que le therapia a medication ficticie debe esser restringite in su application a periodos de augmento de stress.

6. Importante observationes incidental concerneva un gruppo special de patientes con reactiones characteristicamente vage e un gruppo de patientes con morbos de plus que 10 annos de duration in qui responsas favorabile esseva obtenite.

SUMMARIO IN INTERLINGUA

(See page 555 for original article)

Incidentia de Co-Existente Hypertension Essential e Maligne Morbos Neoplastic Studio Basate Super le Protocollos Clinic de 509 Patientes Con e 509 Patientes Sin Neoplasmas Maligne

Le incidentia de hypertension essential—definite primarimente per le criterio de pressiones diastolic de 100 mm Hg o plus—esseva determinate in le protocollos de 509 patientes clinic con neoplasmas maligne e in le protocollos de 509 subjectos de controlo sin neoplasmas maligne. Le duo gruppos esseva parallel in distribution de sexo e etate. Hypertension esseva minus commun in homines que in feminas in le serie neoplastic, e tanto in homines como etiam in feminas de iste serie illo esseva minus commun que in le non-neoplastic serie de controlo. Iste resultato es de accordo con previe studios in que hypertension esseva definite minus strictemente.

Le incidentia de hypertension in patientes con morbo neoplastic es etiam basse quando le valores de comparation es calculate super le base de observationes in un population industrial plus tosto que in un gruppo de patientes clinic. Il es possibile que le basse incidentia de hypertension in patientes con morbo neoplastic possede un signification plus profunde, sed iste question non pote esser elucidate sin extense studios epidemiologic insimul con studios experimental—in tanto que pertinente technicas es accessibile—del association inter morbo hypertensive e morbo neoplastic.

SUMMARIO IN INTERLINGUA

(See page 568 for original article)

Malaria in Veteranos del Guerra Corean: Un Revista de 128 Admissiones pro Malaria a un Hospital de Veteranos

Durante le annos 1951 a 1954 inclusive, 126 veteranos del Guerra Corean esseva admittite pro malaria al Hospital de Aspinwall del Administration de Veteranos.

Esseva observate un reduction significative in le numero de personas admittite pro malaria post le institution in augusto 1952 de therapia a primaquina in massa pro le personal militar. Dece-/cinque personas qui apparentemente habeva recipite primaquina durante lor retorno al Statos Unite disveloppava subsequentemente manifestationes clinic de malaria.

Le malaria observate in veteranos del Guerra Corean, in comparation con illo observate in veteranos del secunde Guerra Mundial, esseva characterisate per un plus longe periodo de latentia, un plus alte frequentia de splenomegalia, e un plus basse frequentia de false reactiones serologic de syphilis. Chloraquina se monstrava efficace in alleviar le symptomas.

BOOK REVIEWS AND NOTICES

PERIPHERAL VASCULAR DISEASE. By A. J. BARNETT, M.D., M.R.C.P. (LOND.), M.R.A.C.P., Assistant Director, Alfred Hospital Clinical Research Unit, Melbourne, and J. R. E. FRASER, M.D., M.R.A.C.P., Sometime Registrar, Alfred Hospital Clinical Research Unit, Melbourne. Pp. 219; 70 ills. Melbourne: Melbourne University Press; New York: Cambridge University Press, 1955. Price, $9.50.

THIS is not a textbook but a monograph based on the authors' experience with peripheral vascular problems. The many case histories exemplifying many various disorders are the most valuable features of this volume. However, the discussions are brief and at times not sufficiently thorough. There are some confusing statements such as the following example on page 157: "Although it is possible to restore the lumen of structurally blocked vessels by a vasodilating agent, if the resistance can be reduced, the blood flow will be increased." The statement on page 119 that intermittent claudication is rare in women is certainly open to question. Indeed in the table on page 121, two out of three females listed among 30 patients with chronic arterial insufficiency had claudication. There should be more complete discussions of arterial grafting, lower aortic thrombotic occlusion and translumbar aortography. Many of the photographs are good but several are valueless and only add to the cost of an overpriced book. N. L.

U. S. ARMY MEDICAL DEPARTMENT: VASCULAR SURGERY IN WORLD WAR II. Edited by DANIEL C. ELKIN, M.D., AND MICHAEL E. DEBAKEY, M.D. Pp. 465; illustrated. Washington: U. S. Government Printing Office, 1955.

THIS is an exhaustive review of the treatment of vascular casualties in World War II. The organization of the book appears to be quite good. Among the introductory portions there are articles referring to methods of handling vascular injuries, with particular reference to organization of specific centers, and methods of examination, followed by methods of treatment of vascular injuries. There are many case reports included in the work which were found to very adequately illustrate the subject being discussed. The methods of arterial repair done at the time are quite thoroughly discussed and treatment of aneurysm and fistulae and posttraumatic circulatory disorders are very well covered. The use of sympathectomy as related to wounds of trauma, received particular attention.

The book provides good basic material and can be highly recommended to those interested in vascular surgery. R. T.

TUBERCULOSIS IN THE ARMY OF THE UNITED STATES IN WORLD WAR II: AN EPIDEMIOLOGICAL STUDY WITH AN EVALUATION OF X-RAY SCREENING (V. A. Medical Monograph). By ESMOND R. LONG, M.D., Director, The Henry Phipps Institute, University of Pennsylvania, and SEYMOUR JABLON, A.M., Statistician, Follow-Up Agency, Division of Medical Sciences, National Research Council, Washington, D. C. Pp. 88; 15 ills. Washington: U. S. Government Printing Office, 1955. Price, $1.50.

THIS monograph describes, in great statistical detail, an analysis of the induction and separation chest roentgenograms and the personnel records of approximately 3000 men inducted into the Army between 1 July 1942 and 1 July 1945, and discharged because of disability due to tuberculosis between 1 May 1943 and 31 December 1946. The "control" group consists of 3000 men who served between the same dates but were not discharged because of tuberculosis.

After careful study of the material, including as many as five readings of chest roentgenograms, the authors conclude that approximately half of the men discharged for tuberculosis had the disease in roentgenographically detectable form at the time of induction. The incidence of tuberculosis was excessively high in prisoners-of-war. Men serving in the Medical Department developed the disease at a higher rate than those in any other branch of service. Tall, thin men developed tuberculosis more frequently than men of other physical types, which harks back to the old concept of a "phthisical habitus."

There are interesting observations on the accuracy of single versus multiple interpretations of chest films, re-reading of films by the same radiologist, and the possible use of the tuberculin test in the induction survey.

R. C.

DOCTORS' OFFICES & CLINICS: MEDICAL & DENTAL. BY PAUL HAYDEN KIRK AND EUGENE D. STERNBERG. Pp. 218; illustrated. New York: Reinhold Publishing Corp., 1955. Price, $12.00.

HERE is a book that will fascinate all physicians and dentists and should be particularly helpful to those who are planning new offices, be these for one physician or a large group. All essential information including cost of materials and heating is provided and the profuse illustrations, some in color, leave nothing to the imagination as to plans, furnishings and photographs of finished structures. R. K.

PRACTICE IN RADIOTHERAPY. Edited by SIR ERNEST ROCK CARLING, LL.D., F.R.C.S., F.R.C.P., F.F.R., Consulting Surgeon, Westminster Hospital, B. W. WINDEYER, M.B., B.S., D.Sc., F. R. C. S., F.R.A.C.S., F.F.R., Professor of Radiology, University of London, and D. W. SMITHERS, M.D., F.R.C.P., F.F.R., Professor of Radiotherapy, University of London. Pp. 549; 142 ills. St. Louis: C. V. Mosby Co., 1955, and London: Butterworth & Co., 1955. Price, $20.00.

THIS text is divided into a part on treatment (Part II) which is completely adequate, covering all of the major radiotherapeutic applications in an acceptable manner.

The book is particularly distinguished, however, by its Part I, "General Problems in Radiotherapy," which make it of universal usefulness in teaching nonradiologists the elements of radiation physics, radiobiology, and the technical devices available for use in radiotherapy, including radioisotopes. The reviewer believes this section to be without equal as a single source of orientation in the field of radiotherapy and its basis in physics, biology and techniques.

Also deserving especial praise, and endorsement to all who deal in the presentation of results of cancer treatment, is a final chapter on this subject, with specific emphasis on staging. If this chapter's lessons were learned and practiced widely, it would constitute a major advance in the understanding, and therefore treatment, of all cancer. R. R.

ATLAS UND KURZGEFASSTES LEHRBUCH DER PHONOKARDIOGRAPHIE UND VERWANDTER UNTERSUCHUNGSMETHODEN. BY K. HOLLDACK AND D. WOLF, Medical and Pediatric Departments, University of Heidelberg. Pp. 171;179 ills. Stuttgart: Georg Thieme Verlag, 1956 (Intercontinental Medical Book Corporation, New York, U.S. Agents). Price, $17.00.

THE topic covers registration of heart sounds, of pulsations of arteries and veins, of respiration and esophageal pulsations. The physical basis, technique and apparatus for phonocardiography are presented with a detailed discussion of filter systems. There is a practical guide on how to obtain graphs and how to interpret them. The graphs are partly registered photoelectrically, partly by means of direct writer, usually three obtained by different filters, and are correlated with the electrocardiographic graph. Following a presentation of the methodology, there are presented varying physiologic and pathologic conditions: 1) extrasounds (split first and second, mitral opening, systolic click, third, pulmonary and aortic distension, atrial, protodiastolic); 2) significance of first sound and of mitral opening snap in the evaluation of mitral stenosis; 3) acquired valvular lesions, including the Austin-Flint and Graham-Steell murmurs; 4) congenital cardiovascular anomalies; and 5) clicking sounds, musical murmurs, functional cardiac murmurs, sound phenomena with air embolism, extracardiac murmurs (pericardial, cardiopulmonary), vascular murmurs. There are 223 well chosen references. The quality of the illustrations is superior and the legends offer minute descriptions and interpretations. This atlas is well recommended. H. R.

DOCTOR AND PATIENT AND THE LAW. BY LOUIS J. REGAN, M.D., LL.B., Professor of Legal Medicine, College of Medical Evangelists, Clinical Professor of Forensic Medicine, School of Medicine, University of Southern California. 3rd ed. Pp. 716. St. Louis: C. V. Mosby Company, 1956. Price, $12.50.

THIS most interesting and informative volume follows the general outline in legal courses given in medical schools. The author is one particularly adept in writing such a book inasmuch as he holds both medical and legal degrees. The material is carefully catalogued and although the subject matter is voluminous it is done in such a concise manner as to make it a practical hand book for both physicians and attorneys as well as laymen.

Interest in the book is heightened by the inclusion of excellent excerpts from leading cases bearing on the subject matter under discussion and the citations thereto. This method of presentation makes the book as

useful to the practicing attorney as to the medical doctor.

The author deals with the question of malpractice at length both setting forth what constitutes malpractice as well as suggested methods of avoiding the stigma of such involvements. Also treated in detail are the physician-patient relationship, agency, liability of hospitals and the potential court room activity involving a physician which would include expert testimony, expert witnesses, evidence and proofs generally. Separate chapters have been devoted to medical legal problems of dentists and nurses.

It is regretted that the author did not include more information regarding the dispensing and prescribing of narcotic drugs. No reference is made to Public Law No. 729 of the 83rd Congress regarding oral prescriptions for such narcotic drugs or preparation as the Commissioner of Narcotics shall find to possess "little or no addiction liability." S. F.

NEW BOOKS

Corticotropin: Its Pharmacologic Effect in Man and Practical Therapeutic Utilization. By Gordon B. Myers, M.D., and William Q. Wolfson, M.D., Wayne University College of Medicine and Detroit Receiving Hospital. Pp. 80; 6 ills. Detroit: Wayne University Press, 1955. Price, $1.75.

A concise statement of the effects and uses of this important medicament that puts at the disposal of the physician the essential matter gleaned from a vast literature. R. K.

White Coolies. By Betty Jeffrey. Pp. 104; illustrated. New York: Philosophical Library, Inc., 1955. Price, $3.75.

This is the first published account of the experiences of an Australian Army Nursing Sister in the hands of the Japanese as a prisoner-of-war from February, 1942, to the end of the War. It is a grim story of privation, starvation and ill-treatment, but with a touch of humor and spirit in a diary that makes fascinating reading. R. K.

A Study of Two Levels of Bread Enrichment in Children's Diets. By Pauline Beery Mack, Alice Knapper Milsom, and Paul L. Carney, Texas State College for Women and the Pennsylvania State University. Pp. 92; 39 ills. Champaign, Ill.: Child Development Publications, Vol. 18, Serial No. 57, No. 2, 1953. (Society for Research in Child Development, Inc.), 1955.

The studies described were planned to determine whether the addition of enriched bread to the diets of children whose regular dietary intake approached adequacy would be responsible for any improvement in health status. The extensive studies are described in detail. W. N.

Proceedings of the Third Medical Conference of Muscular Dystrophy Associations of America, Inc. Edited by H. D. Bouman, M.D. Pp. 324; 25 ills. Baltimore: Williams & Wilkins Co., 1955.

This is a collection of papers read at the Third Medical Conference on Muscular Dystrophy. All of them have previously appeared in the American Journal of Physical Medicine.

They cover the basic biochemistry and physiology of muscle as well as the clinical aspects of the dystrophy problem. One of the authors points out that one of the aims of the symposia has been to furnish those interested with new ideas for research. This, the reviewer feels sure will be accomplished. He is also inclined to think of this volume as primarily of interest to the laboratory and basic science research man or woman. Unfortunately, of course, there is no report of effective treatment. S. G.

The Mechanisms of Healing in Human Wounds. By Shattuck W. Hartwell, M.D., Ph.D., in Surgery, F.A.C.S., F.I.C.S., Chief of Surgery, Mercy Hospital, Muskegon, Michigan. Pp. 166; 44 ills. Springfield, Ill.: Charles C Thomas, 1955. Price, $4.75.

In this monograph the author undertakes to correlate certain clinical and tissue factors involved in the healing of human surgical wounds, burns, ulcers, and donor sites. Many of the concepts offered are based upon the author's own observations and experience. It is regrettable that histochemical, enzymatic, metabolic and other studies are not included to support some of the hypotheses presented. Perhaps this is due to the incomplete bibliography of 41 references, only 9 of which were published since 1930. However, surgeons and others concerned with the problems of wound healing may be interested in various practical aspects of the material in this volume. C. Z.

NEW EDITIONS

A Textbook of Pathology. By E. T. Bell, M.D., Emeritus Professor of Pathology, University of Minnesota. 8th ed. Pp. 1028; 545 ills. and 5 plates in color. Philadelphia: Lea & Febiger, 1956. Price, $14.50.

The appearance of yet another, the eighth, edition attests the continued popularity and usefulness of this well done text. Much of the material has been rewritten and much has been added to bring the work fully up-to-date. Worthy of note is the purpose of the author to furnish

a text which shall continue to serve the student in his clinical training as well as in his preclinical years. The format and illustrations are up to their usual high standard. R. K.

Synopsis of Gynecology. By Robert J. Crossen, M.D., Associate Professor of Clinical Gynecology and Obstetrics, Washington University School of Medicine. 4th ed. Pp. 255; 132 ills. St. Louis: C. V. Mosby Co., 1956. Price, $5.25.

The fourth edition of Crossen's "Synopsis of Gynecology" like the first is a condensation of his standard size text and includes most of the material covered in the large volume. It is directed toward medical students and general practitioners and, therefore, is more didactic than most standard texts. Suggestions for diagnosis and treatment are for the most part clearly and specifically presented; operative procedures are usually mentioned and evaluated but descriptions of the procedures are properly omitted. The section describing the methods of examination is particularly good.

In the condensation certain subjects have been given a disproportionate amount of emphasis, particularly in a book directed toward nonspecialists. For instance, 14 of the total 245 pages are devoted to the discussion of congenital anomalies as compared to 12 pages for abnormalities in menstrual bleeding and dysmenorrhea, and about 2½ for infertility. The discussion of radiation therapy for cancer of the cervix, in which the author attempts to summarize dosage, the calculations of tissue dosage and methods for applying radium, is confusing. As an indication of how often patients with cervical cancer are operated upon the author quotes a study published in 1949. There are a number of typographical errors; for instance, the clinical classification of carcinoma of the cervix is included under "Biopsy" without a separate heading.

This type of book is undoubtedly valuable for medical students and family physicians because it can be used as a ready and practical reference. If there were a bibliography, however, it might stimulate some students to pursue the subject further. If all the important material concerning a subject can be presented in a small book which the student is apt to read how important is the extensive reference text which he can't afford to buy and may rarely open? J. W.

THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

Published Monthly. Illustrated.

Subscription price: 1 year $10.00; 2 years $18.00.

(One year subscription to Canada, South and Central America, Philippines and Spain, $10.36; all other countries $11.14.)

All foreign subscriptions payable in advance in United States dollars.

Business Correspondence: Lea & Febiger, 600 S. Washington Sq., Philadelphia 6, Pa.

NOTICE AND INSTRUCTIONS TO CONTRIBUTORS

Manuscripts intended for publication in The American Journal of the Medical Sciences, and correspondence should be sent to the Editor:
Dr. Richard A. Kern, Temple University School of Medicine, Philadelphia 40, Pa.

Articles are accepted for publication in The American Journal of the Medical Sciences exclusively, except in the case of subsequent publication in Society proceedings.

Manuscripts should be typewritten on one side only, of good quality paper and should be double spaced with liberal margins. The author's chief position and, when possible, the Department from which the work is produced should be indicated in the subtitle.

Illustrations accompanying articles should be numbered and have typed captions bearing corresponding numbers. For identification they should also have the author's name written on the margin or back. Line drawings and charts should be prepared with black India ink. Special arrangements can be made for printing color plates, elaborate tables or an excessive number of illustrations.

References should be numbered and at the end of the articles arranged alphabetically according to the name of the first author and should be complete, that is, author's name, journal, volume, page and year (in Arabic numbers).

Return Postage should accompany all manuscripts but will be returned to the author if the manuscript is accepted.

100 Reprints will be supplied gratis. Covers will be omitted on all articles. Orders of additional reprints will be supplied in multiples of 100. An order form showing cost of reprints is sent with proof. Individual reprints can usually be obtained by writing directly to the author.